RAPID CONSTRUCTION OF POLYCYCLIC ETHER SKELETONS USING TWO-DIRECTIONAL OLEFINIC ESTER CYCLIZATION; TOTAL SYNTHESIS OF (-)-BREVENAL AND EFFORTS TOWARDS THE SYNTHESIS OF YESSOTOXIN AND ADRIATOXIN

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

Marine polycyclic ether natural products have attracted considerable attention from the scientific community because of their unique structures and intriguing biological activities. Olefinic ester cyclization is a highly efficient way to synthesize cyclic enol ethers, which are versatile synthetic precursors to polycyclic ether natural products and analogues. Chapter 1 describes our approach for rapid construction of polycyclic ether skeletons using a two-directional olefinic ester cyclization strategy.

(-)-Brevenal is a pentacyclic polycyclic ether natural product isolated from the marine dinoflagellate *Karenia brevis*. Brevenal has shown to antagonize the toxic effect of brevetoxins in vivo, and can be potentially used as a lead compound for therapeutic treatment of mucociliary dysfunction. Chapter 2 describes our total synthesis of brevenal using a convergent and flexible esterification/olefinic ester cyclization strategy.

Yessotoxins are a class of marine polycyclic ether natural products isolated from dinoflagellate and/or shellfish. Although over 40 of yessotoxins have been identified and characterized, their biological properties are still not clear due to very limited availabilities from natural source. Chapter 3 describes our efforts towards the synthesis of yessotoxin and one of its analogues, adriatoxin. The A-F and F-I ring systems of yessotoxin and adriatoxin were successfully synthesized utilizing both our iterative cyclic enol ether/*C*-glycoside formation and convergent esterification/olefinic ester cyclization strategies.

To my family for their unconditional love and support.

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LIST OF ABBREVIATIONS

[α]	specific rotation
Ac	acetyl
AIBN	2,2'-azobisisobutyromitrile
Bn	benzyl
Bu	butyl
*n*Bu	*neo*-butyl
*t*Bu	*tert*-butyl
^{o}C	degrees Celsius
calcd	calculated
COSY	correlation spectroscopy
CSA	10-camphorsulfonic acid
d	day(s); doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
dr	diastereomeric ratio
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	di-*iso*-butylaluminum hydride
DMAP	4-dimethylaminopyridine

DMDO	dimethyldioxirane
Et	ethyl
EtOAc	ethyl acetate
EI	electron impact
ESI	electron spray ionization
g	gram(s)
HMPA	hexamethylphosphoramide
h	hour(s)
Hz	hertz
IR	infrared spectroscopy
J	coupling constant (in NMR)
KHMDS	potassium hexamethyldisilazide
LDA	lithium di-*iso*-propylamide
LHMDS	lithium hexamthyldisilazide
L-selectride	lithium tri-*sec*-butylborohydride
M	moles per liter
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
MOM	methoxymethyl
MS	mass spectrometry; molecular sieves

m/z	mass to charge ratio (in mass spectrometry)
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million (in NMR)
PPTS	pyridinium *p*-toluenesulfonate
*i*Pr	*iso*-propyl
Py	pyridine
q	quartet (in NMR)
R_f	retention factor (in TLC)
rt	room temperature
s	singlet (in NMR); second (s)
t	triplet (in NMR)
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonoyl
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydropyrane
TIPS	tri-*iso*-propylsilyl

TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TsOH	*p*-toluenesulfonic acid
VGSC	voltage gated sodium channels

ACKNOWLEDGEMENTS

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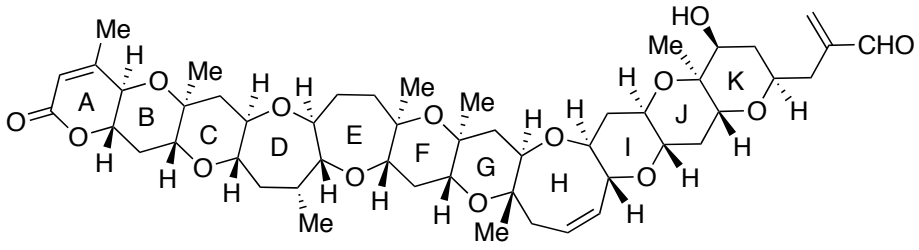
Finally, I wish to thank my parents for their unconditional love and support throughout my whole life. They have always been my greatest source of inspiration and consolation. Without their encouragement and support, none of the work presented here would have been possible.

CHAPTER 1

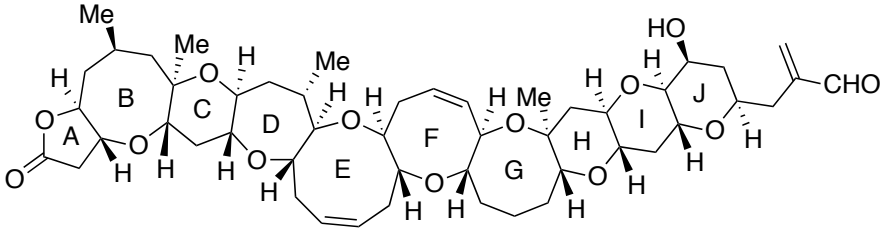
RAPID CONSTRUCTION OF POLYCYCLIC ETHER SKELETONS USING TWO-DIRECTIONAL OLEFINIC ESTER CYCLIZATION

Introduction

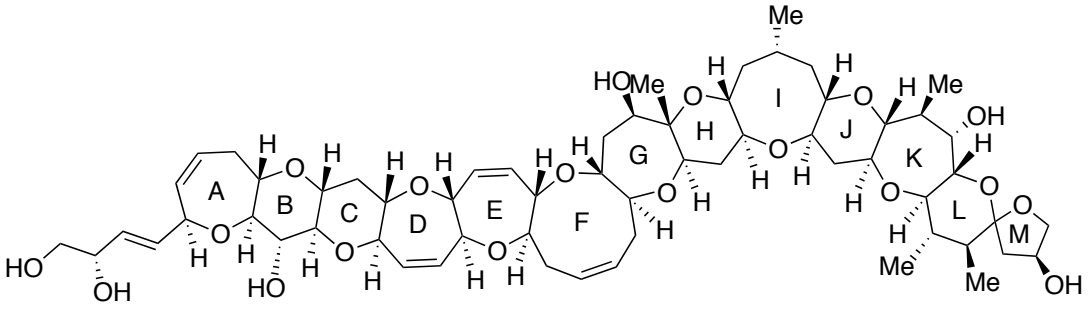
In 1981, Nakanishi and co-workers reported the isolation and structure of brevetoxin B (**1.1**, Figure 1.1), which introduced a new class of marine natural products, the ladder-shaped polycyclic ethers into the scientific community.[1] Since then, this family of natural products has attracted considerable attention from both synthetic chemists and biologists because of their unique structures and intriguing biological properties.[2] The representative members of this class of natural products include brevetoxins A (**1.2**) and B,[3] ciguatoxin (**1.3**),[4] gymnocin A (**1.4**),[5] gambierol (**1.5**),[6] gambieric acid A (**1.6**),[7] yessotoxin (**1.7**),[8] and brevenal (**1.8**) (Figure 1.1).[9] Structurally, they all contain a contiguous *trans*-fused polycyclic ether ring skeleton, which gives them a characteristic ladder-shaped appearance. Biologically, despite the common polycyclic ether motif, they exhibit very diverse and potent properties. For example, the brevetoxins and ciguatoxins display potent neurotoxicity toward fish and human beings, while gambieric acids exhibit potent antifungal activity with only moderate toxicity against mammals.[10,11] These interesting biological behaviors have fascinated chemists and biologists for nearly three



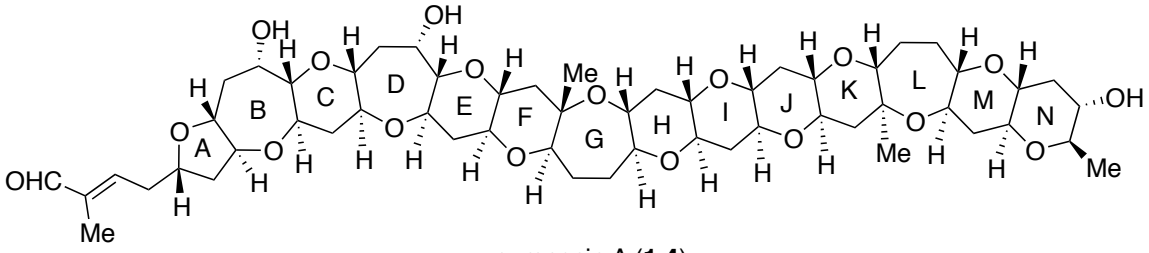
brevetoxin B (**1.1**)



brevetoxin A (**1.2**)

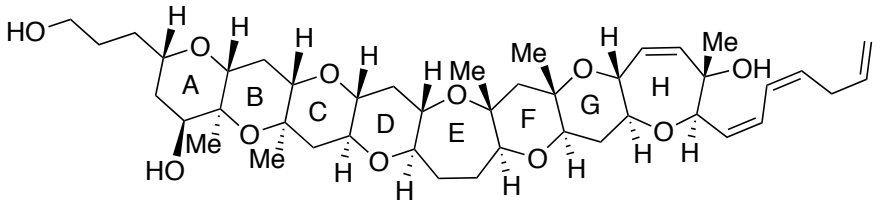


ciguatoxin (CTX, **1.3**)

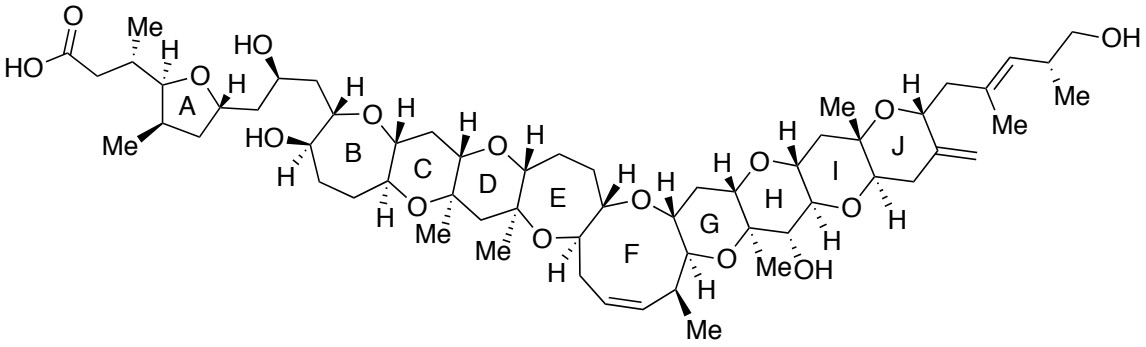


gymnocin A (**1.4**)

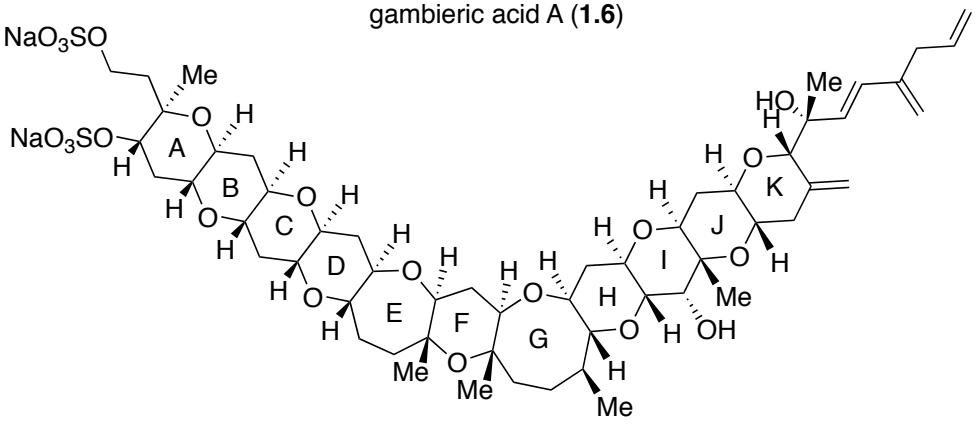
Figure 1.1. Representative members from the polycyclic ether natural product family



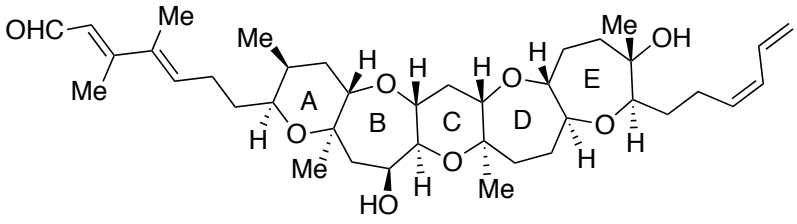
gambierol (**1.5**)



gambieric acid A (**1.6**)



yessotoxin (**1.7**)



brevenal (**1.8**)

Figure 1.1 (cont'd).

decades. Unfortunately however, the biological properties of many of these polycyclic ether natural products still have not been fully investigated because of their very limited availability form natural sources. Chemical synthesis may serve as a solution to the supply problem of these natural products.

In addition to the need of polycyclic ether natural products for further biological research, there is also a demand for the synthesis of analogues of these natural products for the study of their structure-activity relationships (SAR). So far, the target proteins have been identified only for the brevetoxins, ciguatoxins, and gambierol.[12,13] Brevetoxins and ciguatoxins bind and activate voltage-gated sodium channels of excitable membranes,[12] while gambierol binds and blocks voltage-gated potassium channels.[13] Based on these studies, it has been proposed that polycyclic ether natural products apply their biological activity through binding to different ion channels. The synthesis and biological evaluation of analogues of polycyclic ether natural products will not only provide great insight for the identification of the required structural motifs for activity, but they will also be very useful in the study of the behaviors of ion channels.

Motivated by their unique structures and intriguing biological activities, a number of research laboratories have been interested in the chemical synthesis of polycyclic ether natural products.[14] In 1995, Nicolaou and co-workers reported the total synthesis of brevetoxin B, which was the first synthesis of a highly complex molecule from the polycyclic ether family.[15] Since then, major progress has been made in this field due to the developments of novel synthetic methodologies and coupling strategies from different laboratories. These efforts have culminated in the total syntheses of brevetoxin A, synthesized independently by Nicolaou (1998)[16] and Crimmins (2009);[17] ciguatoxin

CTX3C by Hirama (2001);[18] gambierol by Sasaki (2002),[19] Kadota/Yamamoto (2002),[20] and Rainier (2005);[21] brevetoxin B by Nakata (2004)[22] and Kadota/Yamamoto (2005);[23] gymnocin A by Sasaki (2003);[24] and brevenal by Sasaki (2006),[25] Kadota/Yamamoto (2009),[26] and Rainier (2011).[27]

The Rainier laboratory has been active in the synthesis of polycyclic ether natural products and their analogues since the 1990s.[28] Our strategy for constructing the contiguous polycyclic ether motif is based on an iterative cyclic enol ether/*C*-glycoside formation sequence (Figure 1.2). Each iteration generally involves 4 steps starting from a cyclic enol ether: (1) addition of a carbon nucleophile to a glycal anhydride; (2) esterification; (3) olefination of an ester; (4) and ring-closing metathesis. To date, this strategy has been successfully applied in our total syntheses of hemibrevetoxin B,[29] gambierol,[21] brevenal[27] and other structurally related architectures.[30]

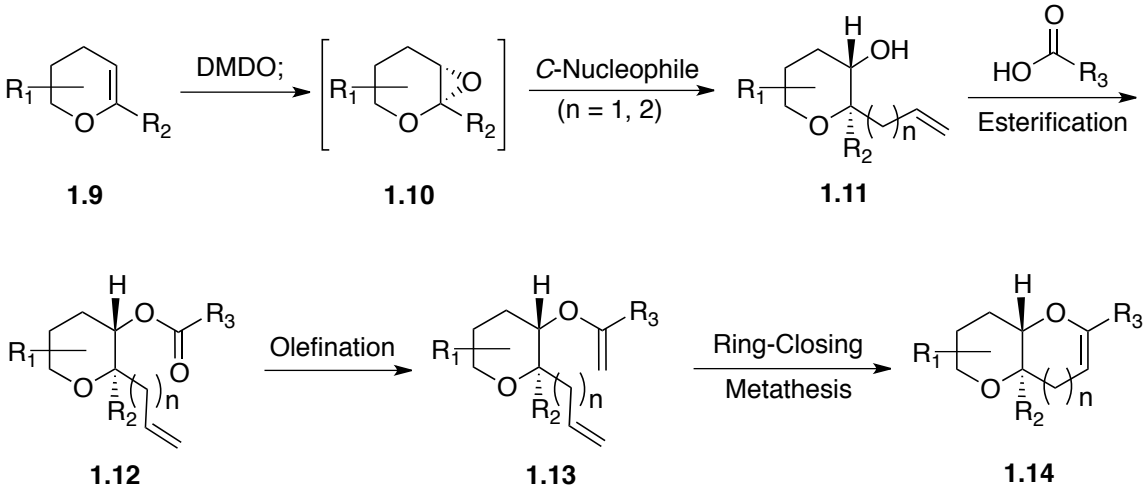
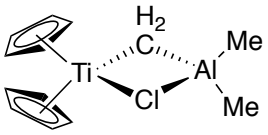


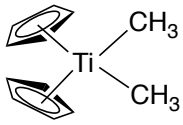
Figure 1.2. Our iterative strategy towards polycyclic ether compounds

Synthesis of Cyclic Enol Ethers Using a Two-Step Protocol

As shown in Figure 1.2, cyclic enol ethers serve as critical intermediates in our approach to polycyclic ether natural products. Meanwhile, they are also very useful synthetic precursors to a variety of other cyclic ether containing bioactive natural products such as nucleoside antibiotics and carbohydrate derivatives.[31] There are a number of methods that have been developed to synthesize cyclic enol ethers.[32] Among them, the two-step sequence shown in Figure 1.2 consisting of olefination of an ester using titanium reagents (Tebbe reagent **1.15**,[33] Petasis reagent **1.16**,[34] or Takai-Utimoto reagent[35]) and ring-closing metathesis using either ruthenium catalyst **1.17**,[36] **1.18**[37] or molybdenum catalyst **1.19**[38] is one of the most efficient ways to make cyclic enol ethers (Figures 1.3 and 1.4).



Tebbe Reagent (**1.15**)

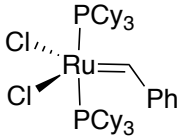


Petasis Reagent (**1.16**)

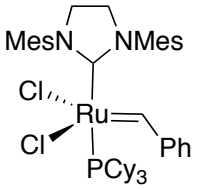
$TiCl_4$, THF, TMEDA, Zn,
$PbCl_2$, $RCHBr_2$

Takai-Utimoto Reagent

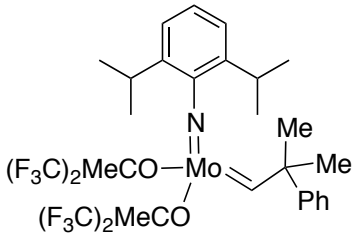
Figure 1.3. Titanium reagents used in olefination of esters



Grubbs' 1st Generation Catalyst (**1.17**)



Grubbs' 2nd Generation Catalyst (**1.18**)



Schrock's Catalyst (**1.19**)

Figure 1.4. Catalysts used in ring-closing metathesis

In 1994, Grubbs and co-workers first used this two-step strategy to make furan and pyran rings. In particular, an antifungal natural product, phytoalexine (**1.23**) was synthesized very efficiently using this approach (Figure 1.5).[32b] The Takai-Utimoto reagent was employed to convert ester **1.20** to acyclic enol ether **1.21**, which was subsequently subjected to Schrock's molybdenum catalyst **1.19** to give cyclic enol ether **1.22**. Hydrogenolysis of the benzyl ethers generated the natural product phytoalexine in excellent yield.

Since then, this two-step approach has been further developed and applied by a number of research groups in their syntheses of natural products, especially of polycyclic ether natural products and saccharides.[39] Depicted in Figure 1.6 are some representative examples. In 1996, Nicolaou and co-workers converted olefinic ester **1.24** using Tebbe reagent **1.15** under ambient conditions to acyclic enol ether **1.25**, which was then transformed to six-membered cyclic enol ether **1.26** using the Tebbe reagent in refluxing THF.[39a] In 1997, Clark and co-workers found that a combination of the Takai-Utimoto

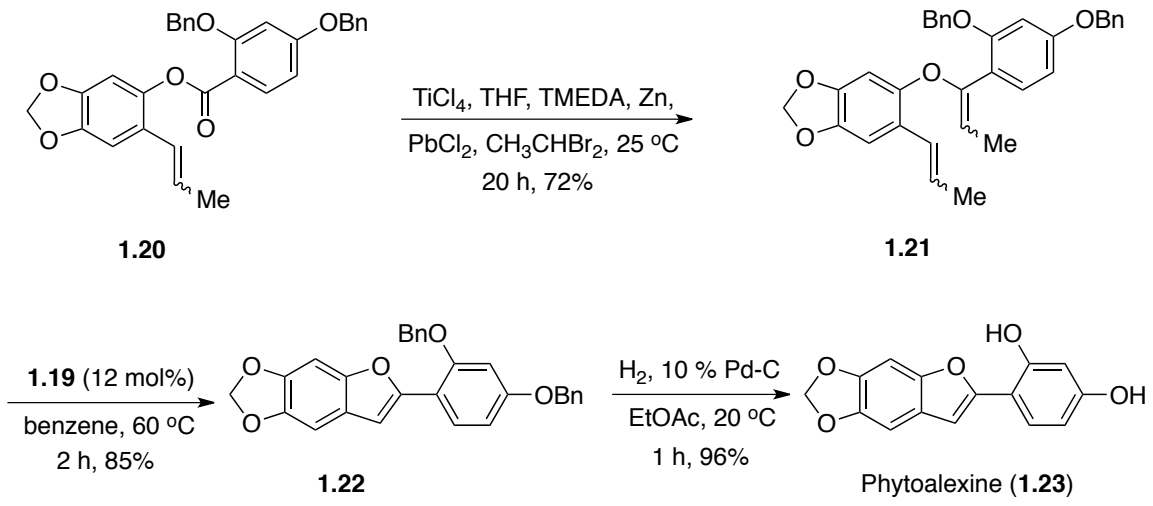


Figure 1.5. Grubbs' synthesis of phytoalexine (**1.23**)

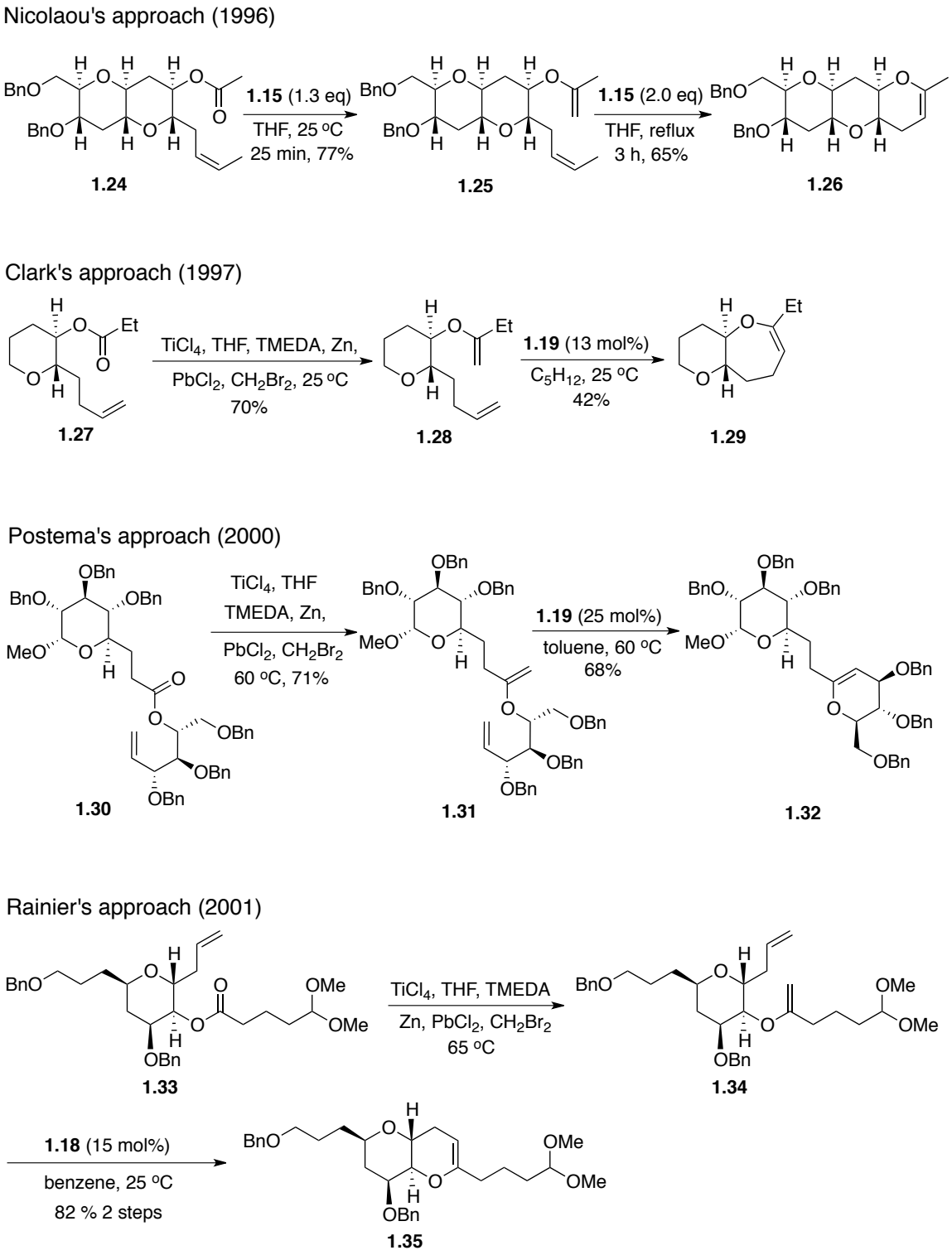


Figure 1.6. Examples of olefination/metathesis strategy in synthesis

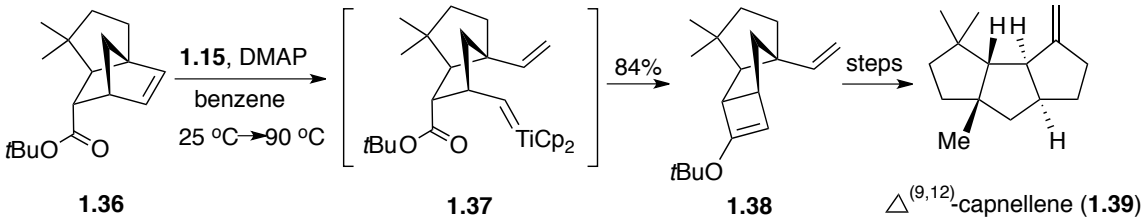
reagent and Schrock's catalyst **1.19** was also amenable in synthesizing seven-membered cyclic enol ethers.[39b] In all cases published up to 2000, the two reactive motifs, olefin and acyclic enol ether, were always attached to an existing ring template, which brought them proximal to one another for facile cyclization. Postema and co-workers first reported that open chain substrates such as **1.30** could also be used in this strategy to generate *C*-disaccharides.[39c] In 2001, Rainier and co-workers first demonstrated that the Grubbs' 2nd generation catalyst **1.18** was capable of effecting ring-closing metathesis of olefinic enol ethers as well.[39d]

Although the described two-step protocol has proven to be very effective in the synthesis of cyclic enol ethers, a more efficient and direct strategy would bypass the acyclic enol ether intermediate and directly convert an olefinic ester to the corresponding cyclic enol ether. There have been only a few examples of direct olefinic ester cyclizations in the literature.[40-45]

Direct Conversion of Olefinic Esters to Cyclic Enol Ethers

The first example was from the Grubbs' laboratory in 1986. In their total synthesis of $\Delta^{(9,12)}$-capnellene (**1.39**), Grubbs and co-workers successfully converted the olefinic ester **1.36** to the cyclic enol ether **1.38** through a ring-opening metathesis and carbonyl olefination reaction sequence using Tebbe reagent **1.15** (Figure 1.7).[40] In this case, they took advantage of the inherent strain of the norbornene system in the starting material. Subsequently in 1993, Grubbs and Fu reported the use of tungsten alkylidene reagent **1.41** to generate cyclic enol ether **1.42** directly from olefinic ester **1.40**.[41] Thus far, this is the only report of direct olefinic ester cyclization using a tungsten catalyst.

Grubbs' approach towards capnellene (1986)



Grubbs and Fu's cyclization using a tungsten catalyst (1993)

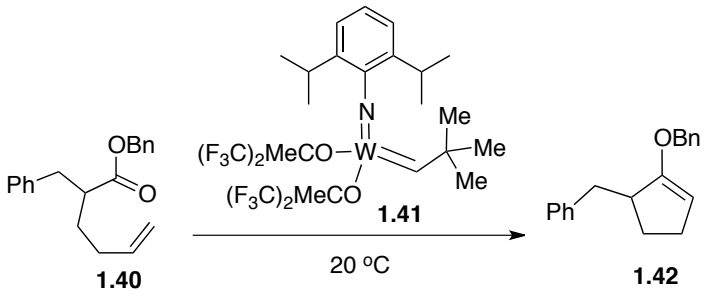


Figure 1.7. Direct olefinic ester cyclization from Grubbs' laboratory

Nicolaou and co-workers later modified the aforementioned Tebbe reagent two-step olefinic ester cyclization and developed a one-pot tandem methylenation and metathesis sequence to synthesize cyclic enol ethers.[39a] They then applied this strategy in the construction of several fragments of maitotoxin (Figure 1.8).[42] Impressive as Nicolaou's one-step protocol was, a number of groups have reported this procedure to give capricious results.[43]

In 2002, Rainier and co-workers reported that when using a modified Takai-Utimoto procedure, a mixture of acyclic enol ether **1.48** and cyclic enol ether **1.51** were obtained in 3:5 ratio from olefinic ester **1.46** (Figure 1.9).[44] More interestingly, when acyclic enol ether **1.48** was isolated and subsequently resubjected to the same reaction conditions, no cyclic enol ether **1.51** was observed. Based on the results, they proposed

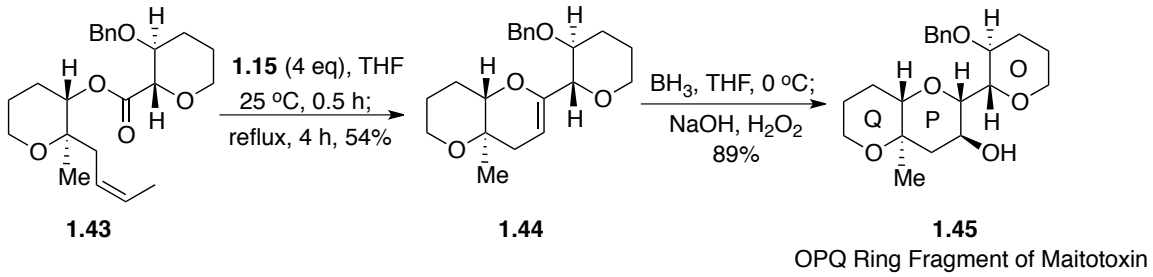


Figure 1.8. Nicolaou's synthesis of the OPQ ring system of maitotoxin

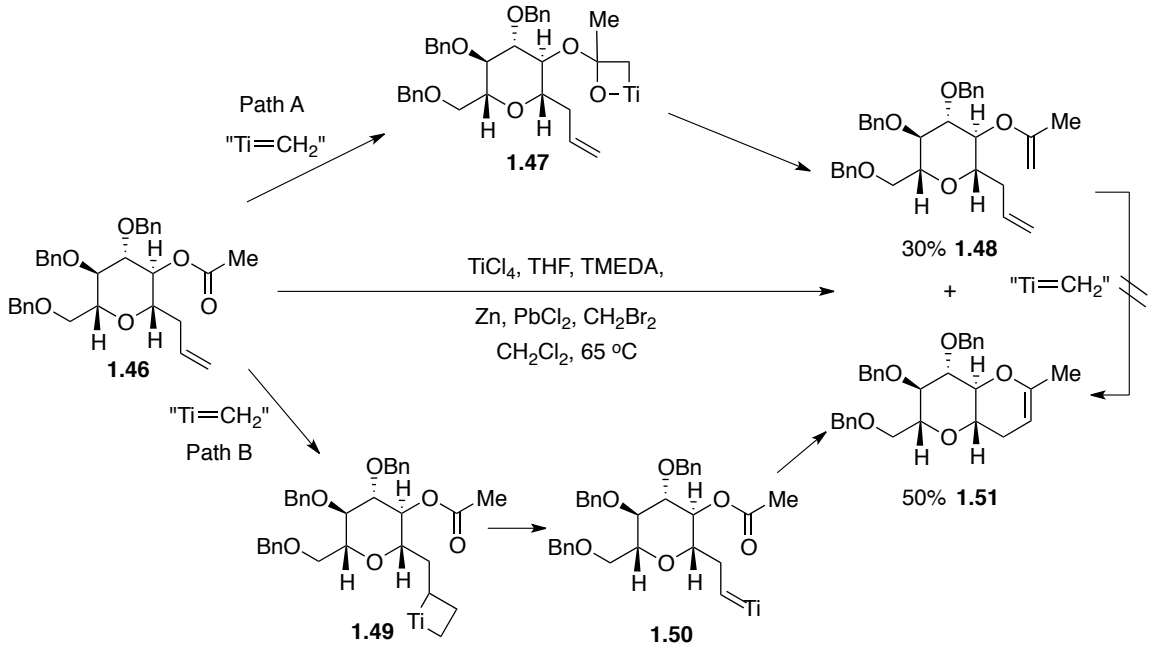
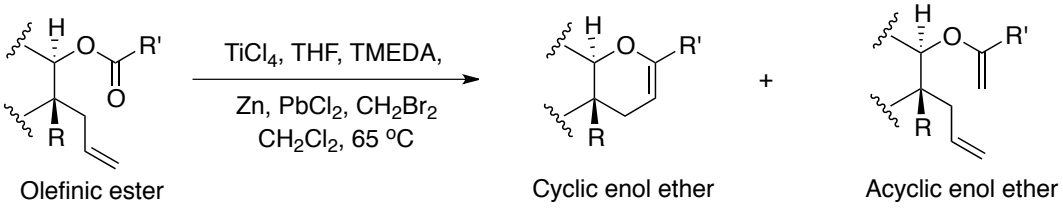


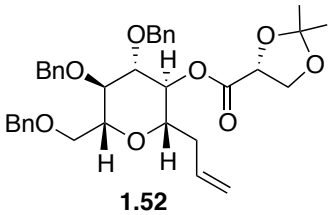
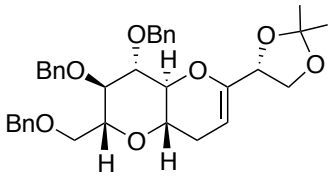
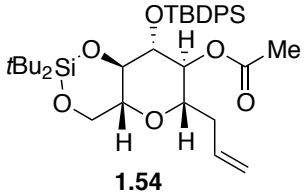
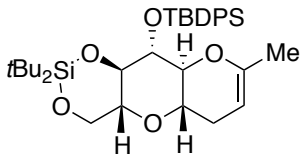
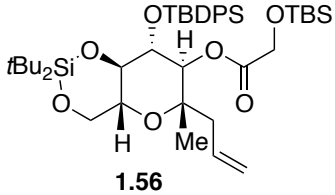
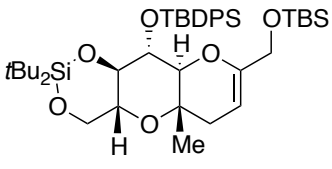
Figure 1.9. Direct cyclic enol ether formation from a modified Takai-Utimoto reaction

that the titanium methylidene reagent generated under the reaction conditions competitively reacts with both the olefin and the ester. If the initial coupling occurs on the olefin, a terminal titanium alkylidene intermediate **1.50** would be generated, which then cyclizes onto the ester to give cyclic enol ether **1.51**. On the other hand, coupling of the reagent with the ester results in the formation of **1.48**. The resulting enol ether does not participate in alkene metathesis under the reaction conditions.

The proposed mechanism was further supported by the cyclization results from a series of elegantly designed substrates (Table 1.1).[45] For substrates with sterically hindered esters and unhindered olefins such as **1.52** and **1.54**, olefin metathesis was more facile than carbonyl olefination, thus cyclic enol ether products **1.53** and **1.55** were predominantly formed. For substrate **1.56**, because of the angular methyl group, the olefin was more hindered than that in **1.54**. As a result, a 1.3:1 mixture of the cyclic and

Table 1.1. Substrate dependence of the Takai-Utimoto reaction



Olefinic ester	Cyclic enol ether product	yield	C:A ratio
 **1.52**	 **1.53**	71%	>95:5
 **1.54**	 **1.55**	84%	>95:5
 **1.56**	 **1.57**	77%	1.3:1

acyclic enol ether products was obtained under the reaction conditions. These results demonstrated the substrate dependence of the Takai-Utimoto cyclization reaction.

Despite these previous efforts, there had not been a general reaction procedure for direct conversion of olefinic esters to corresponding cyclic enol ethers. All previous reactions had been demonstrated to be either substrate-dependent or to give capricious results.

Titanium Ethylidene Reagent-Effected One-Step Olefinic Ester Cyclization

In 2005, in their total synthesis work of the marine polycyclic ether natural product gambierol (**1.5**), Rainier and co-workers reported an interesting result during the synthesis of the E ring (Figure 1.10).[21] When the olefinic ester **1.58** was subjected to the Takai-Utimoto conditions using dibromomethane as the titanium alkylidene source, they observed preferential decomposition of the starting material and only a small amount of

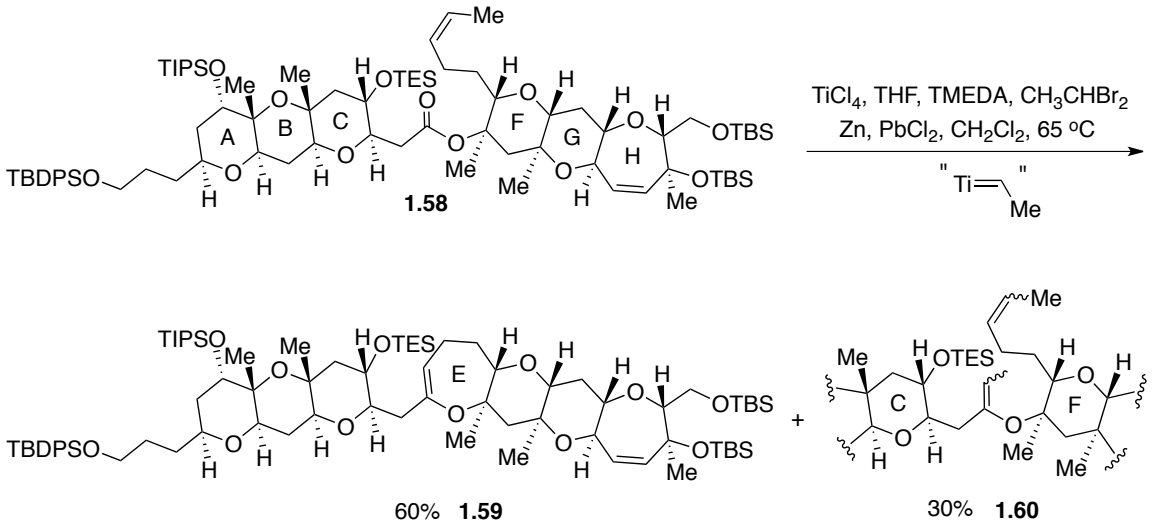


Figure 1.10. Direct olefinic ester cyclization with dibromoethane

desired cyclic enol ether product **1.59** (15-30%). When dibromoethane was employed as the titanium alkylidene source, a 2:1 mixture of cyclic and acyclic enol ether was obtained in good overall yield.

Subsequently, during their synthesis of the A-E ring fragment of another marine polycyclic ether natural product gambieric acid A (**1.6**), Rainier and co-workers found that when olefinic ester **1.61** was subjected to the Takai-Utimoto conditions using dibromomethane, only acyclic enol ether **1.62** was generated, while the use of dibromoethane gave cyclic enol ether **1.64** exclusively from olefinic ester **1.63** (Figure 1.11).[30]

Both of the results listed above demonstrated very different reactivity patterns of different titanium alkylidene reagents towards olefinic esters and implied that the product

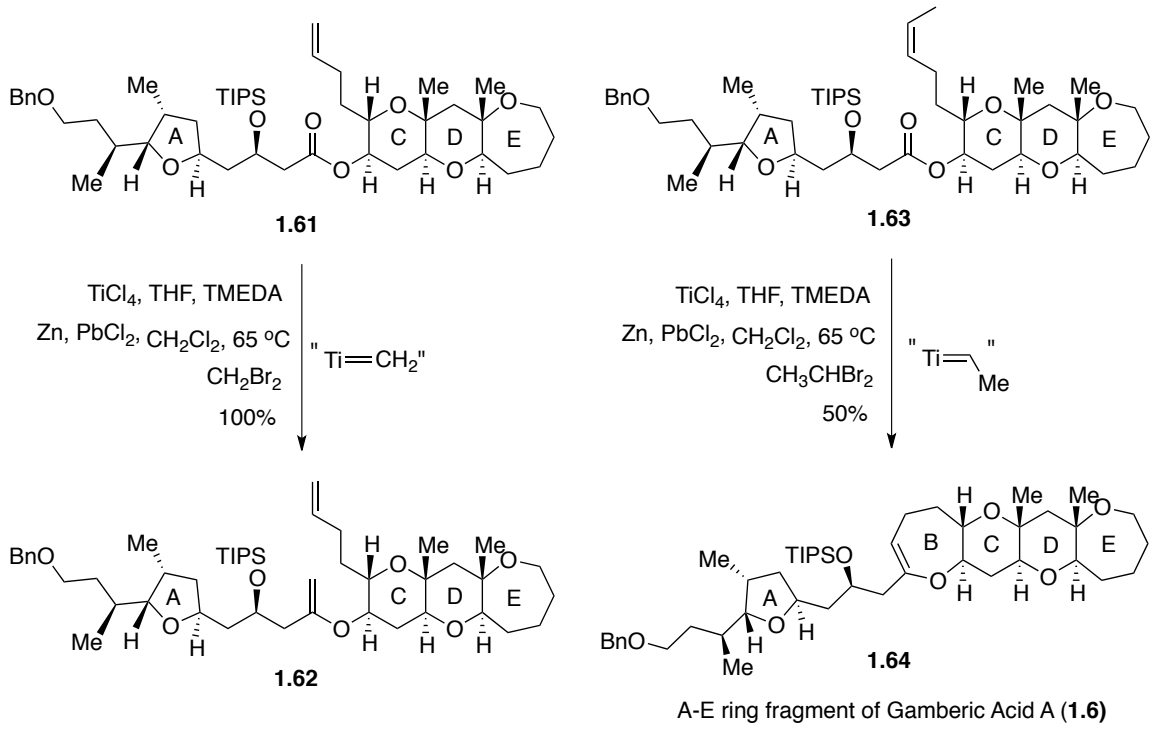
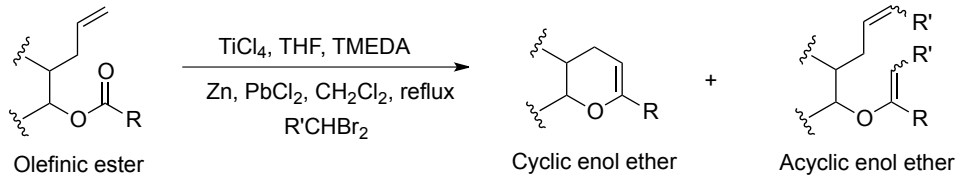


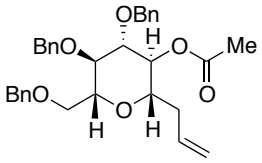
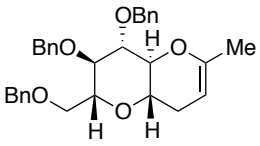
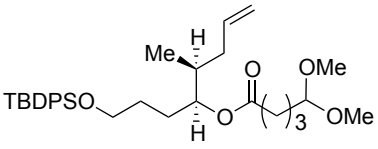
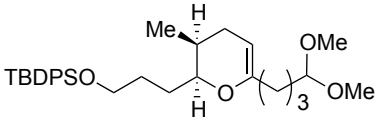
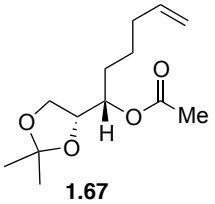
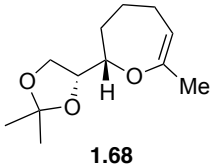
Figure 1.11. Different reaction patterns with different titanium alkylidene reagents

distribution (acyclic vs. cyclic enol ether) could be affected by the nature of the alkylidene reagents. Combined with the proposed mechanism shown in Figure 1.9, it was suggested that the more hindered titanium ethylidene reagent reacted preferentially with the olefin rather than the ester in an olefinic ester, thus leading to a predominant formation of cyclic enol ether product.

Rainier and co-workers further investigated the scope of this reaction and found it to be general and applicable to a broad range of substrates (Table 1.2).[46] As mentioned in Figure 1.9, when olefinic ester **1.46** was subjected to the Takai-Utimoto conditions using dibromomethane, a 3:5 mixture of acyclic and cyclic enol ether was obtained.[44] In sharp

Table 1.2. Comparison of product outcomes using dibromomethane and dibromoethane



Substrate	Cyclic enol ether product	CH_2Br_2	CH_3CHBr_2
 **1.46**	 **1.51**	80% C : A = 5 : 3	75% C : A > 95 : 5
 **1.65**	 **1.66**	70% C : A = 1 : 1	70% C : A > 95 : 5
 **1.67**	 **1.68**	——	82% C : A > 95 : 5

contrast, when dibromoethane was used as the titanium alkylidene source, cyclic enol ether product **1.51** was exclusively obtained in good yield. More impressively, even substrates without a tethered cyclic template such as **1.65** and **1.67** underwent exclusive cyclization under the reaction conditions to give six- and seven-membered cyclic enol ethers. The finding that substitution on the titanium alkylidene reagent could be used to direct reactivity was unprecedented in the literature.

Rainier and co-workers then applied this methodology to olefinic lactone cyclizations and discovered a new way to make all-carbon macrocycles.[47] Both (-)-muscone (**1.73**) and (+)-muscopyridine (**1.74**) were synthesized using this method (Figure 1.12). Also worth mentioning is that the same titanium ethylidene reagent is capable of effecting olefinic-amide cyclizations to make cyclic enamines.[48]

The discovery of the titanium ethylidene-effected olefinic ester cyclization reaction has largely facilitated our total synthesis program toward polycyclic ether natural

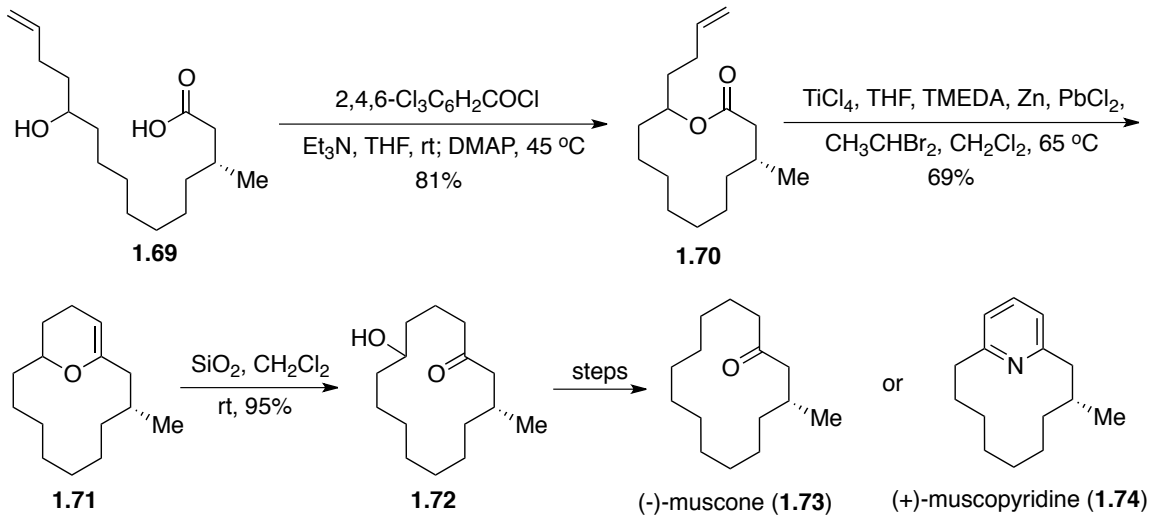


Figure 1.12. Rainier's syntheses of (-)-muscone and (+)-muscopyridine

products.[27,49,50] When compared to the formerly used two-step olefination-metathesis procedure, the new method not only improves the efficiency by shortening the number of steps, but it also eliminates the required column chromatography between the two steps, thus generally leads to a better overall yield of cyclic enol ether products.

Previous Two-Directional Approach towards Polycyclic Ether Natural Products

As mentioned previously, biological studies on polycyclic ether natural products have been hampered by the limited quantities isolated from natural sources. With the newly developed olefinic ester cyclization protocol in mind and also considering the inherent symmetrical nature of these molecules, it occurred to us that our iterative approach to polycyclic ether frameworks would be even more efficient if it were amenable to a two-directional approach where two olefinic esters would undergo cyclization to give two new cyclic enol ethers in one flask.

Several research groups had already demonstrated the power of two-directional approaches toward polycyclic ether natural products.[51] Among them, the strategy of the Clark group was the closest to ours in that it involved a two-directional ring-closing metathesis reaction from dienes or ene-ynes to make cyclic enol ethers using the Schrock or Grubbs' catalysts. Recently, they have applied this methodology to the synthesis of the F-J fragment of gambieric acid A (**1.6**, Figure 1.13).[51e] Their synthesis commenced from D-glucal triacetate **1.75**, which consisted of the H ring of gambieric acid A. In ten steps, **1.75** was converted into dialkynyl ether **1.76**, to which two different cuprate reagents were added stepwise by exploiting the steric difference between the alkynes to give **1.77**.

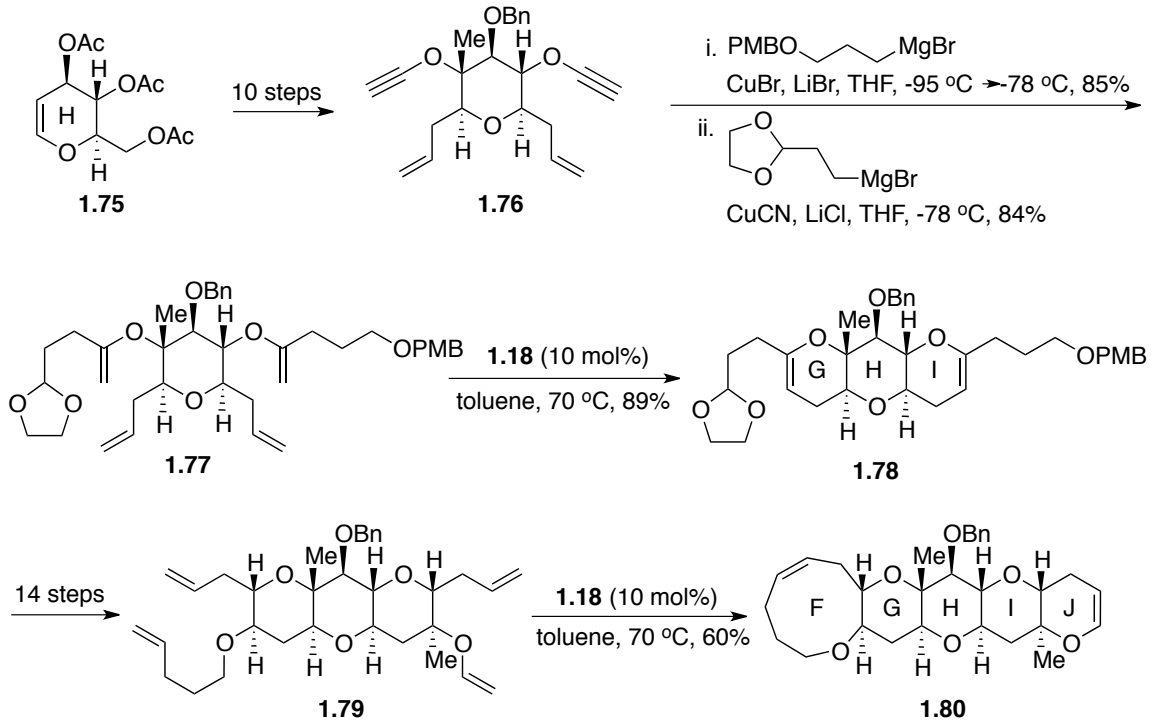


Figure 1.13. Clark's two-directional approach to F-J ring system of gambieric acid A

The critical two-directional ring-closing metathesis was then effected using Grubbs' 2nd generation catalyst **1.18** to simultaneously afford the G and I ring of gambieric acid A. Compound **1.79** was subsequently obtained after 14 steps, to which another two-directional ring-closing metathesis was applied to furnish the F-J fragment of gambieric acid A **1.80**.

Our proposed two-directional approach towards polycyclic ether natural products is different from Clark's in that: (1) the precursors would be olefinic esters rather than dienes or ene-ynes; (2) and the alkylidene reagents used to carry out the cyclizations would be titanium rather than ruthenium or molybdenum. Herein, we described our results of the two-directional olefinic ester cyclization strategy towards the synthesis of polycyclic ether structures.[52]

Results and Discussions

We first chose to test the two-directional olefinic ester cyclization on the readily available dienyl diester **1.85**, which could be obtained in five steps from the known compound **1.81** (Figure 1.14).[51e] Removal of the silylene protecting group revealed triol **1.82**, and the primary alcohol was selectively converted into a triflate with the two secondary alcohols protected as TES ethers in one flask. Allylcuprate addition to the primary triflate and subsequent deprotection of the TES ethers afforded diene **1.84**, which upon acetylation gave the dienyl diacetate cyclization precursor **1.85**.[53]

When dienyl diacetate **1.85** was subjected to our modified Takai-Utimoto reaction conditions using dibromoethane as the titanium alkylidene source, we were pleased to find that the desired olefinic ester cyclizations proceeded smoothly on both sides and that the tricyclic compound **1.86** was formed successfully in 64% yield (Figure 1.15).

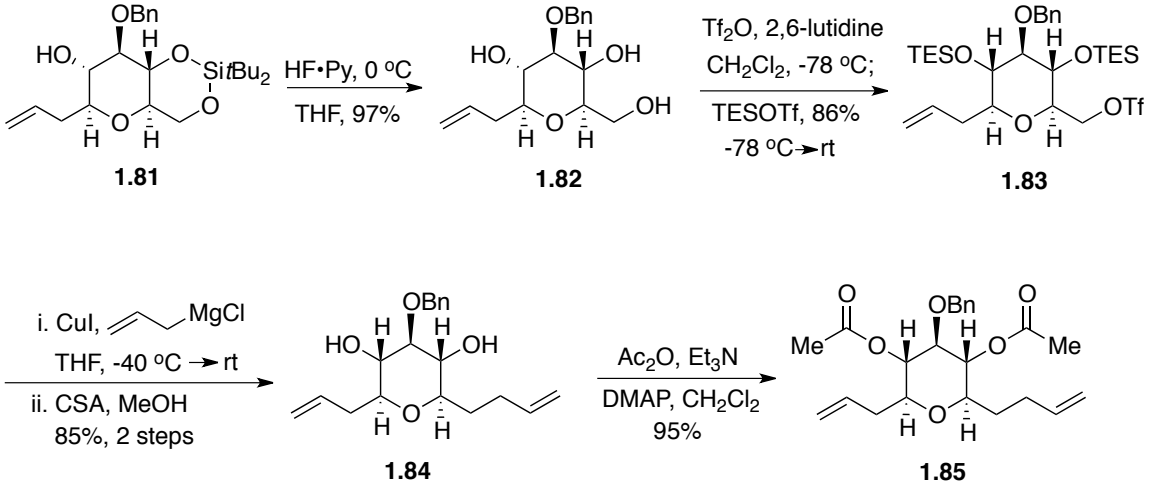


Figure 1.14. Synthesis of the dienyl diester substrate **1.85**

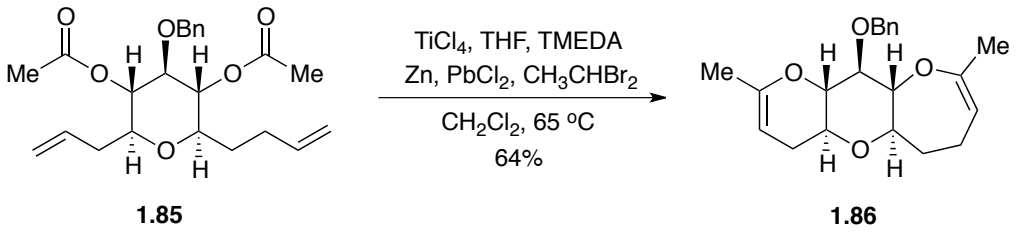


Figure 1.15. Two-directional olefinic ester cyclization of **1.85**

Symmetrical dienyl diester **1.89** and **1.95** were synthesized in a similar fashion to test the generality of this transformation. From primary triflate **1.83**, substitution with lithium trimethylsilylacetylide and subsequent deprotection afforded diol **1.87**.[51e] Partial hydrogenation using Lindlar's conditions and acetylation afforded the cyclization precursor **1.89** (Figure 1.16).[54] Cyclization precursor **1.95** was synthesized from **1.81** (Figure 1.17). Protection of the secondary alcohol as a PMB ether and one carbon homologation through a hydroboration, oxidation, and Wittig olefination sequence gave alkene **1.92**.[55] Removal of the PMB group and silylene group afforded triol **1.93**, which was converted to **1.94** after selective primary triflate formation and TES protection. Coupling of **1.94** with allylcuprate followed by TES removal and acetylation provided cyclization precursor **1.95** in good overall yield.

When dienyl diesters **1.89** and **1.95** were exposed to the titanium ethylidene reagent, both symmetrical tricycles **1.96** and **1.97** were obtained in good yield (Figure 1.18). These results were very exciting to us not only because two new rings could be generated in one transformation, but also because the resulting cyclic enol ethers are important synthetic intermediates that could be further exploited.

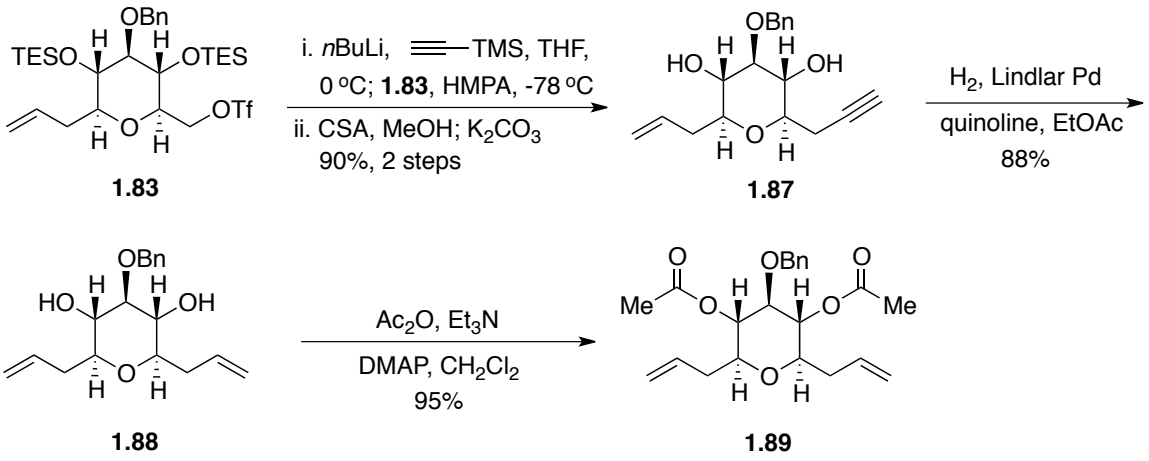


Figure 1.16. Synthesis of the dienyl diester substrate **1.89**

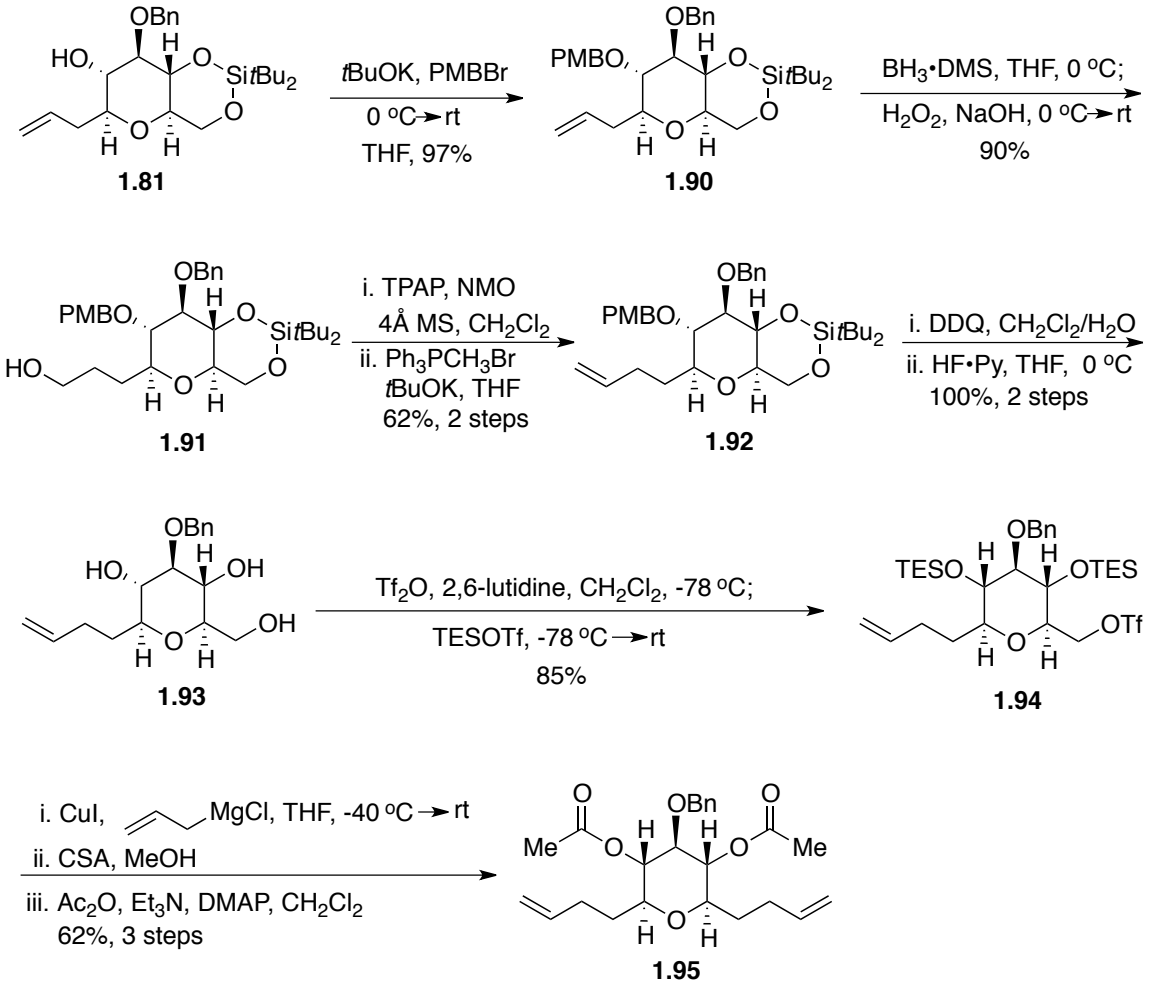


Figure 1.17. Synthesis of the dienyl diester substrate **1.95**

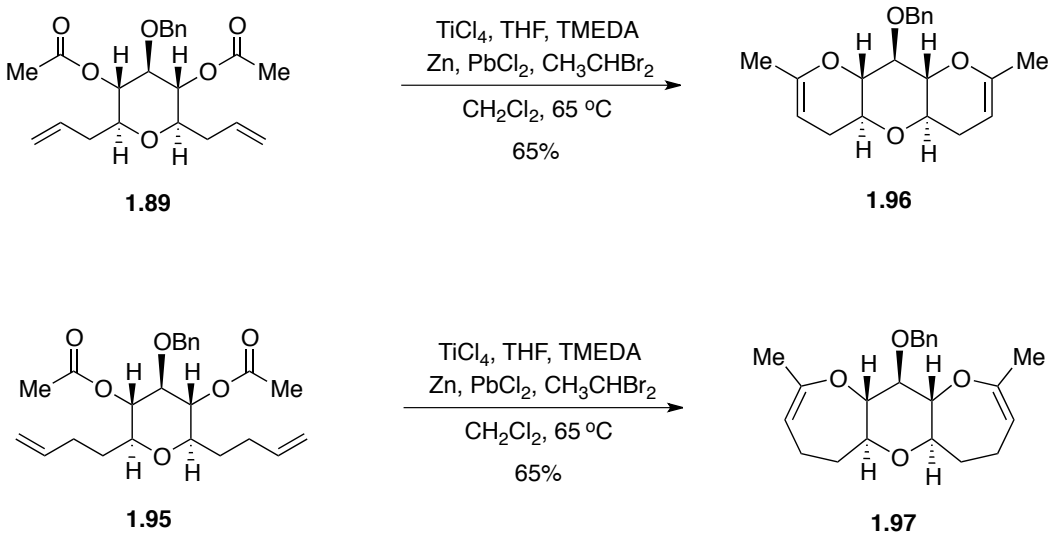


Figure 1.18. Two-directional olefinic ester cyclization of **1.89** and **1.95**

With the above results in hands, we wanted to expand the substrate scope and test our proposition that the generated cyclic enol ethers would undergo further chemical manipulations. Cyclization precursor **1.105** was synthesized from **1.90** as outlined in Figure 1.19. Removal of the silylene group, selective primary triflate formation and protection of the remaining secondary alcohol as TES ether gave **1.99**. Substitition of the primary triflate with lithium trimethylsilylacetylide and removal of the TES and TMS groups afforded hydroxy alkyne **1.100**. Partial hydrogenation using Lindlar's Pd catalyst gave **1.101**, which was coupled with known acid **1.102**[56] using DCC and DMAP to provide ester **1.103**. Deprotection of the PMB group and esterification with acid **1.104**[57] afforded dienyl diester cyclization precursor **1.105**.

When **1.105** was subjected to our modified Takai-Utimoto reaction conditions, tricycle **1.106** was successfully obtained in 60% yield (Figure 1.20). Out of the interest

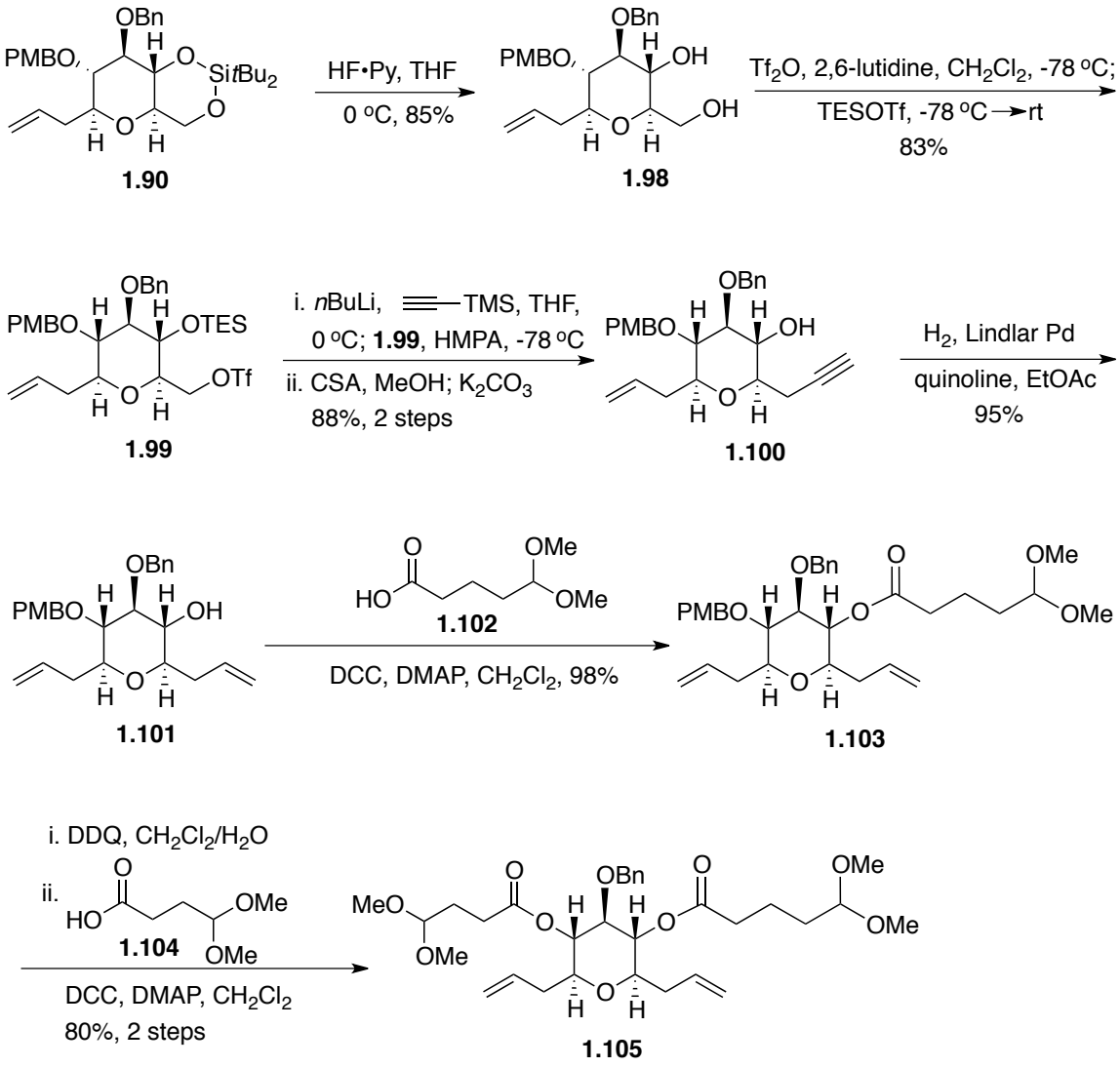


Figure 1.19. Synthesis of the dienyl diester substrate **1.105**

to exploit the cyclization product, we oxidized both enol ethers using DMDO to give the corresponding epoxides, which were subsequently reduced in situ with *i*Bu_2AlH to generate a mixture of diols.[58] Oxidation and equilibration of the resulting ketones with DBU at elevated temperature generated an 8:1 mixture of diketones with **1.108** as the major diastereomer. Reduction of this mixture using Luche's conditions gave the best stereoselectivity in terms of the synthesis of diol **1.109**.[59] Upon treatment of **1.109** with

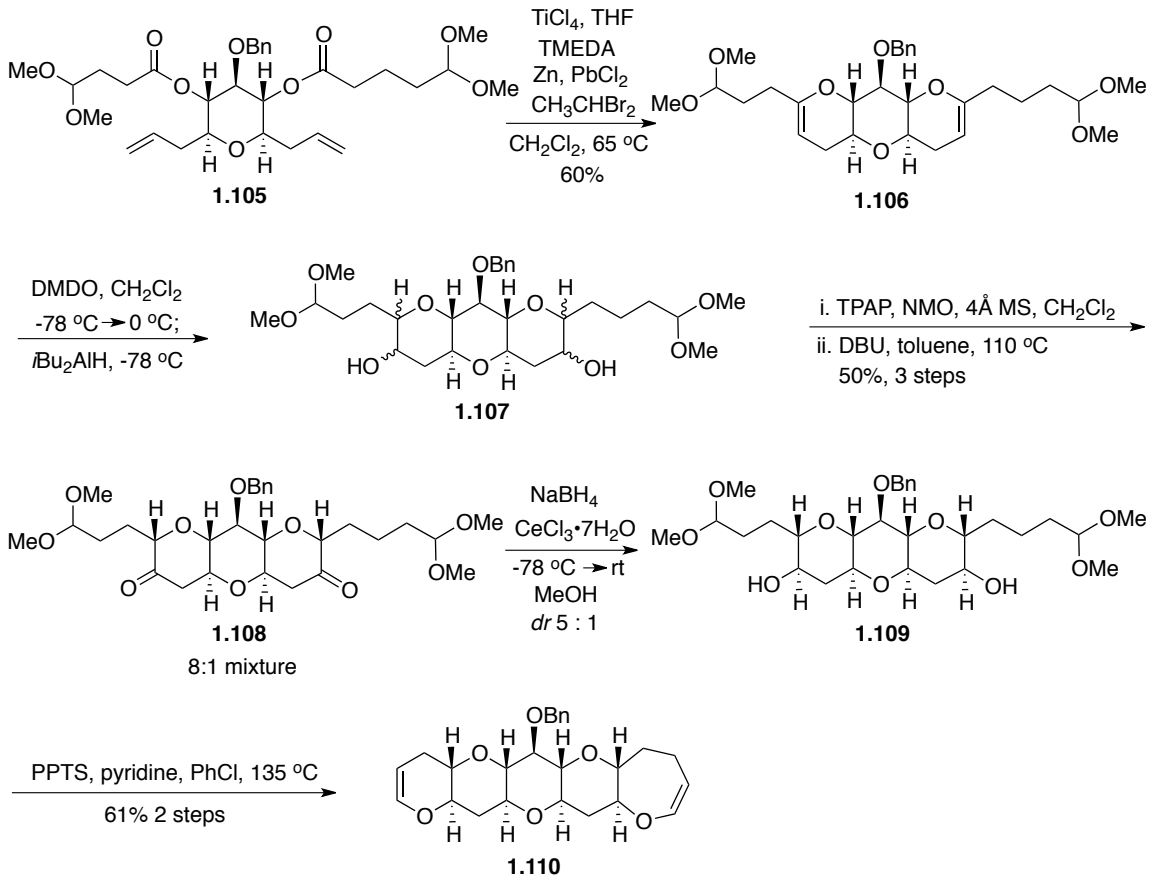


Figure 1.20. Two-directional approach towards pentacycle **1.110**

PPTS, pyridine and heat, both alcohols cyclized onto the pendant acetals and eliminated a molecule of methanol to give the pentacyclic compound **1.110** as a single stereoisomer.[60] Thus, by combining the titanium ethylidene-effected olefinic ester cyclization and the acid-promoted hydroxy acetal cyclization, *trans*-fused pentacycle **1.110** was formed in only six steps from the monocyclic *C*-glycoside **1.105**. The efficient synthesis of pentacycle **1.110** clearly demonstrated the power of the two-directional olefinic ester cyclization reaction in the synthesis of polycyclic ether structures, and gave us impetus to utilize this strategy to synthesize more complicated architectures.

In our previous syntheses of complex marine polycyclic ether natural products and analogues, we developed a convergent strategy that involved esterification between two cyclic ether precursors, olefinic ester cyclization, and reductive cyclization to generate two new cyclic ether rings in the course of coupling (Figure 1.21).[21] With this in mind, it occurred to us that if we could incorporate the two-directional olefinic ester cyclization into the above strategy, we would be able to generate more elaborate polycyclic ether structures rapidly.

To test this proposition, we chose the heptacyclic compound **1.117** as the synthetic target, and the retrosynthetic analysis is shown in Figure 1.22. The B ring and F ring were envisioned to come from **1.118** through reductive cyclization. The C ring and E ring would be generated using the pivotal two-directional olefinic ester cyclization reaction from dienyl diester **1.119**, which could be obtained from the coupling of three functionalized subunits **1.110, 1.121,** and **1.101**.

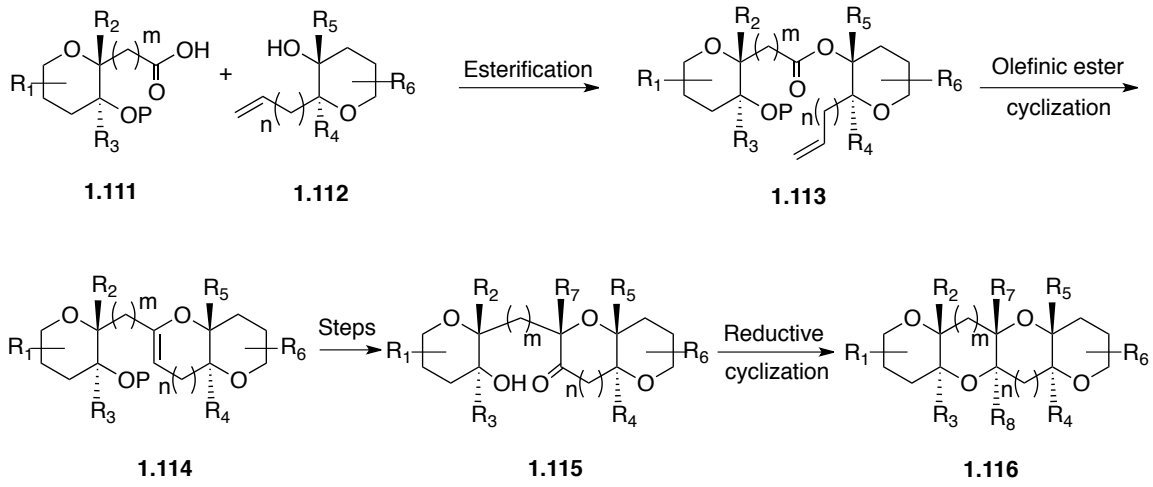


Figure 1.21. Our convergent strategy towards polycyclic ether compounds

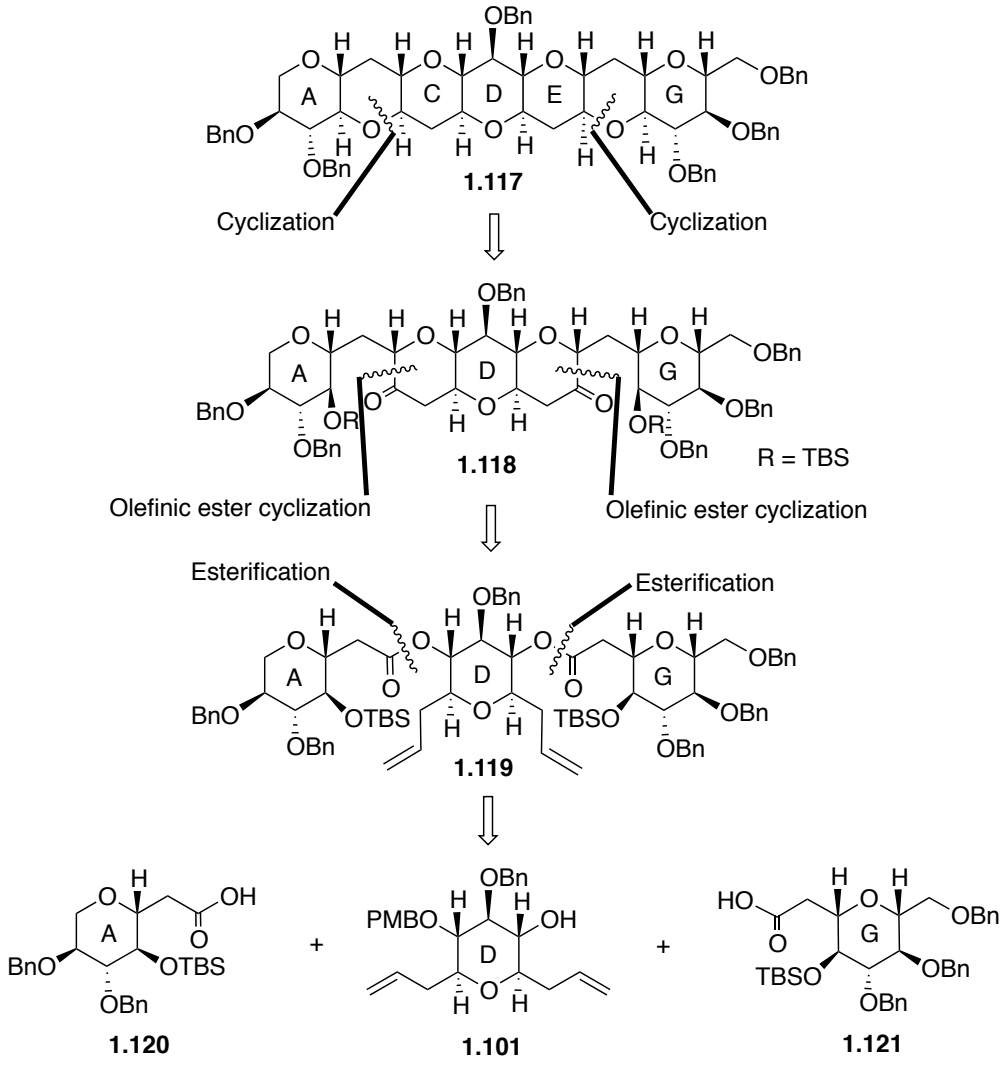


Figure 1.22. Retrosynthetic analysis of heptacycle **1.117**

The A ring acid **1.120** was synthesized from the known D-glucal derivative **1.122** (Figure 1.23).[51e] Epoxidation of the enol ether with DMDO and in situ reduction of the resulted epoxide with *i*Bu_2AlH generated secondary alcohol **1.123**, which was subsequently protected as a benzyl ether. The silylene protecting group was removed using HF•Py to give diol **1.124**, in which the primary alcohol was converted into a triflate and the secondary alcohol was protected as TBS ether. Substitution of the primary

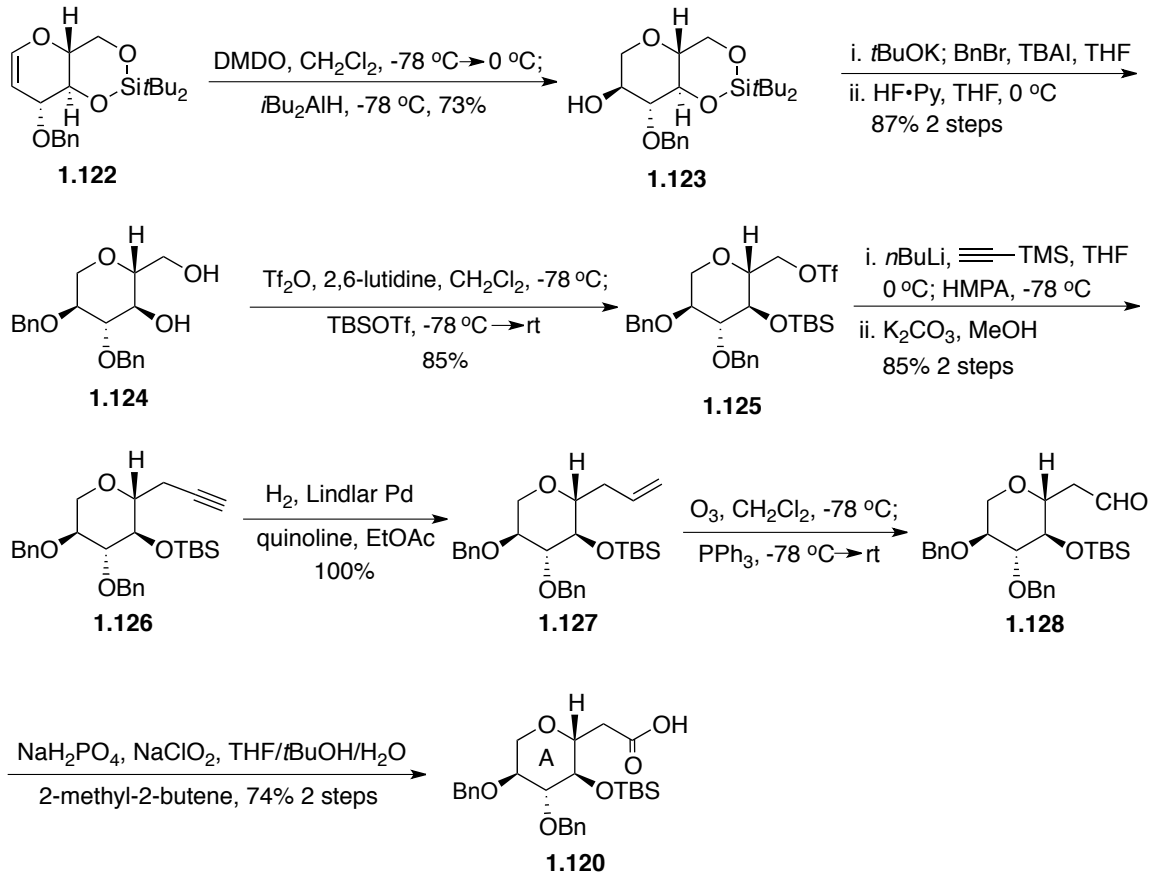


Figure 1.23. Synthesis of the A ring coupling precursor **1.120**

triflate with lithium trimethylsilylacetylide, removal of the TMS group, and partial hydrogenation provided alkene **1.127**. The alkene was then oxidatively cleaved using ozonolysis to give the corresponding aldehyde, which was further oxidized using Pinnick's conditions to provide the A ring coupling precursor **1.120**.[61]

The synthesis of the G ring acid **1.121** commenced from known compound **1.129** (Figure 1.24).[28] Protection of the secondary alcohol as a TBS ether and subsequent oxidative cleavage of the alkene generated aldehyde **1.131**, which was further oxidized to the G ring coupling precursor **1.121** using Pinnick oxidation.

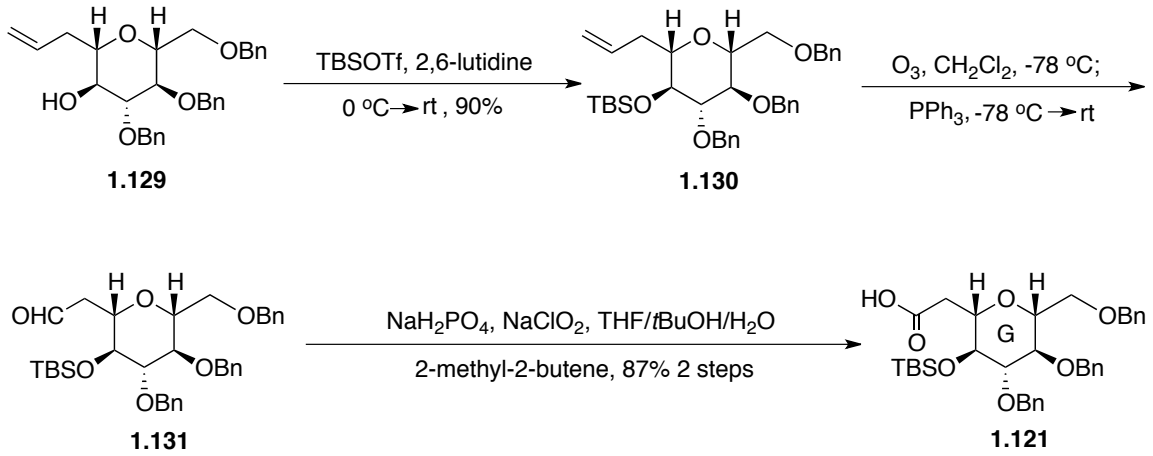


Figure 1.24. Synthesis of the G ring coupling precursor **1.121**

The coupling started from the central D ring alcohol **1.101** and the G ring acid **1.121** (Figure 1.25). Esterification under Yamaguchi's conditions successfully furnished ester **1.132** in 87% yield.[62] After removal of the PMB group using DDQ, a second Yamaguchi esterification with the A ring acid **1.120** was performed to give dienyl diester **1.119**. When **1.119** was subjected to the titanium ethylidene reagent, the two-directional olefinic ester cyclization proceeded smoothly to give the tricyclic compound **1.134** in 50% yield.

With the CDE ring in hand, both enol ethers in **1.134** were oxidized using DMDO to give the corresponding epoxides, which were subsequently reduced in situ with *i*Bu_2AlH to give diol **1.135** in 65% yield as a single stereoisomer (Figure 1.26). Interestingly, under the same reaction conditions, the corresponding diols were obtained as a mixture of diastereomers in the case of bis-enol ether **1.106** (Figure 1.20). The stereochemistry of **1.135** was confirmed using ^1H NMR after converting the secondary alcohols into the corresponding acetates.

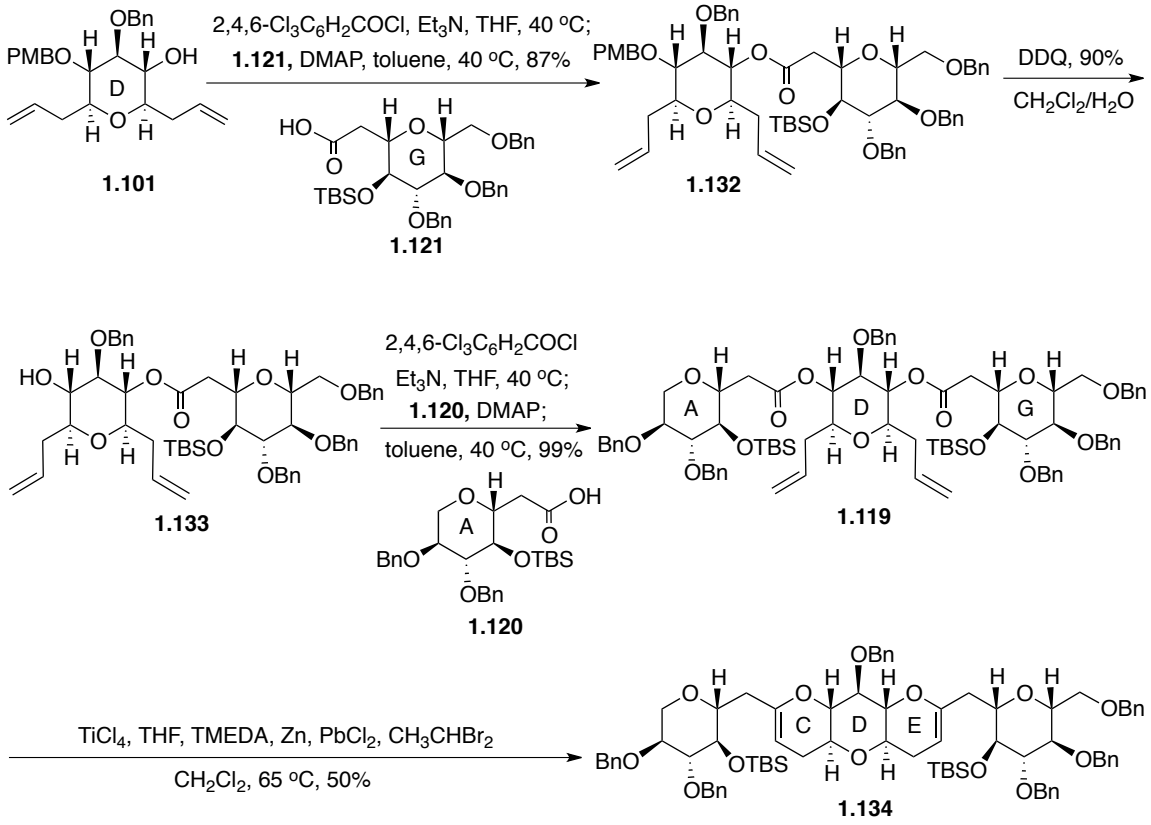


Figure 1.25. Coupling of the three subunits **1.101**, **1.120**, and **1.121**

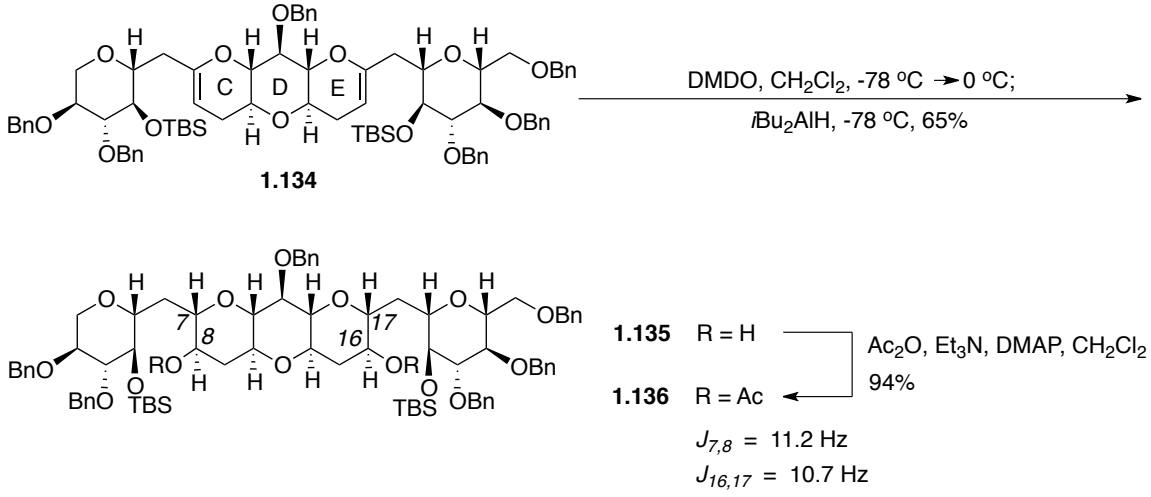


Figure 1.26. DMDO oxidation on the C and E ring enol ether

Oxidation of diol **1.135** revealed diketone **1.118** (Figure 1.27). The TBS groups on both sides were removed using HF•Py, and the generated free alcohols simultaneously cyclized onto the corresponding ketones to form bis-hemiketal **1.137**. Upon treatment with $Zn(OTf)_2$ and EtSH, both hemiketals in **1.137** were converted to *O,S*-mixed ketals, which were subsequently reduced under free radical conditions using Ph_3SnH and AIBN to give the heptacyclic compound **1.117** with good overall yield.[63] Thus by utilizing the highly efficient two-directional strategy, only six synthetic transformations were required to convert the monocyclic *C*-glycoside precursor **1.119** to the heptacyclic compound **1.117**.

With this powerful strategy, we are currently in the process of the synthesis of the *des*-methyl analogue of gambierol **1.139** from three coupling subunits **1.143**, **1.144**, and **1.145** (Figure 1.28). This synthesis is different from the previous ones in that the central subunit **1.144** already contains two fused cyclic ether rings, which we believe will provide us with more information on the substrate scope of the two-directional olefinic ester cyclization reaction. In addition, we hope the biological tests of the final product **1.139** will give us a better understanding of the SAR and the ion channel-binding behaviors of gambierol analogues.

Conclusion

To summarize, this chapter has described a highly efficient two-directional olefinic ester cyclization strategy towards the synthesis of polycyclic ether frameworks. Not only is the strategy promising in the total synthesis of marine polycyclic ether natural products and their analogues, there is also prospect to use this strategy to build libraries

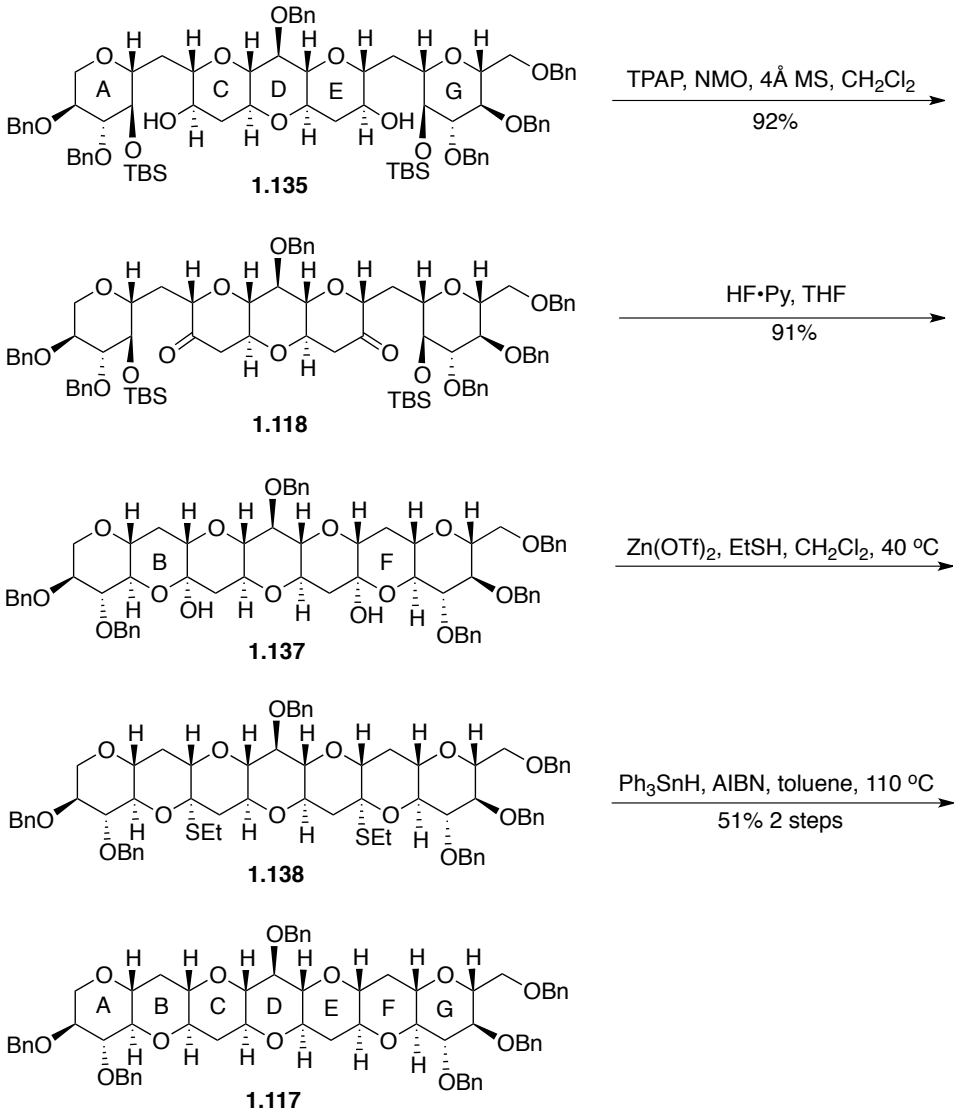


Figure 1.27. Synthesis of heptacycle **1.117**

of polycyclic ether structures to study the binding functions of ion channels. The synthesis of a gambierol analogue using this approach is currently underway in our group. In addition, we propose that with differently functionalized side chains, differentiation of the two terminals can be achieved, which will give us more flexibility and control in the synthesis of polycyclic ether architectures. Efforts to verify this proposition are currently underway as well.

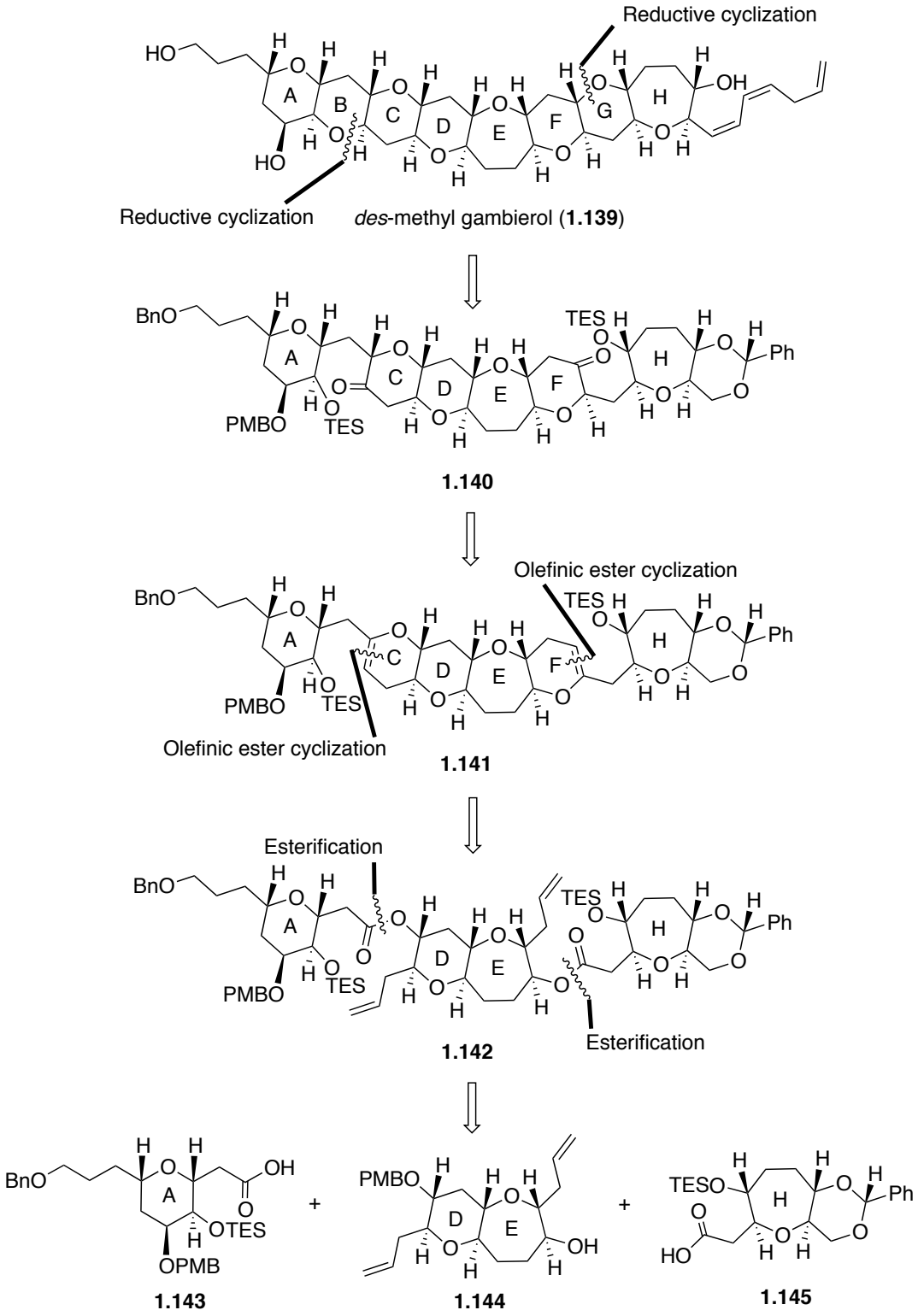


Figure 1.28. Retrosynthetic analysis of *des*-methyl analogue of gambierol **1.139**

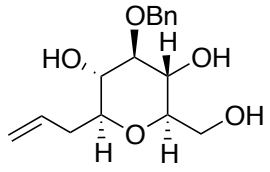
Experimentals

NMR spectra were recorded on Varian Inova-400 MHz, Varian Inova-500 MHz or Varian VXR-500 MHz spectrometers. Chemical shifts were reported in δ, parts per million (ppm), relative to benzene (7.16), chloroform (7.27), or dichloromethane (5.32) as internal standards. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass spectrometer. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Optical rotations were obtained on a Perkin-Elmer Model 343 polarimerter (Na D line) using a microcell with 1 dm path length. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin: Oxford, 1966). Dichloromethane, 2,6-lutidine, triethylamine, TMEDA, chlorobenzene and pyridine were distilled from CaH_2. Tetrahydrofuran and diethyl ether were dried from the sodium ketyl of benzophenone and distilled before use. Zinc dust (<10 μm, Aldrich) was activated by washing with 5% hydrochloric acid, H_2O, methanol, and ether and dried in vacuo overnight. All other reagents were used without further purification. Unless otherwise noted, all reactions were performed under a nitrogen atmosphere in flame-dried glassware using standard syringe, cannula, and septa apparatus. Concentration refers to removal of solvent under reduced pressure (house vacuum at *ca.* 20mm Hg). Analytical thin–layer chromatography (TLC) was performed on silica gel plates (0.25 mm) precoated with a fluorescent indicator. Flash chromatography was performed using 40–63 μm silica gel (200 X 400 mesh).

Procedures and Characterizations

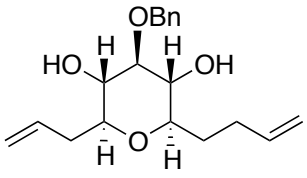
The characterization and procedures for compounds **1.81**, **1.122**, and **1.129** were previously published.[28,51e]

General procedure for two-directional olefinic ester cyclization. (As 0.10 mmol substrate was used.): A two-necked flask fitted with a condenser was cooled to 0 ^{o}C and charged with CH_2Cl_2 (21 mL) followed by $TiCl_4$ (0.35 mL, 3.20 mmol). To the resulting solution was added THF (1.69 mL, 19.2 mmol) dropwise at which time the solution turned bright yellow. The addition of THF was followed by the dropwise addition of TMEDA (2.90 mL, 19.2 mmol) resulting in the formation of a brown solution. The ice bath was removed and the mixture was allowed to stir for 15 min. Activated Zn dust (468 mg, 7.20 mmol) and $PbCl_2$ (105 mg, 0.38 mmol) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3-5 min. To the slurry was transferred a solution of the dienyl diester (0.10 mmol) and CH_3CHBr_2 (0.29 mL, 3.20 mmol) in CH_2Cl_2 (5 mL) via cannula. The reaction mixture was then heated to reflux for 2 h before it was cooled to 0 °C and quenched with sat. K_2CO_3 (aq., 1.0 mL). After stirring for 30 min at 0 °C, the resulting mixture was filtered through a piece of filter paper. The filtrate was concentrated and further purification was performed by flash chromatography.



1.82

Preparation of triol 1.82. To a solution of **1.81** (0.17 g, 0.39 mmol) in THF (10 mL) at 0 °C in a plastic bottle was added a solution of HF•Py (0.78 mL of 1.0 M solution in THF, 0.78 mmol) dropwise. The reaction was quenched after 2 h with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (2:1 to 1:1 hexanes:ethyl acetate) provided 0.11 g **1.82** (97%) as a colorless oil. R_f 0.40 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +3.9° (c = 1.08, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.29 (m, 5H), 5.86 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1H), 5.15 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.07 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.90 (d, *J* = 11.8 Hz, 1H), 4.82 (d, *J* = 11.7 Hz, 1H), 3.80 (dd, *J* = 11.7, 3.4 Hz, 1H), 3.71 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.57 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.40-3.18 (m, 5H), 2.70-2.50 (m, 3H), 2.24 (ddd, *J* = 14.6, 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 134.6, 129.0, 128.3, 128.2, 117.6, 86.6, 79.2, 78.8, 75.1, 73.5, 71.0, 62.6, 36.3; IR (neat) 3408 (broad), 3072, 2912, 1642, 1497, 1454, 1360, 1213, 1093, 917 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{16}H_{22}O_5Na$ 317.2 ($M+Na^+$), found 317.0.



1.84

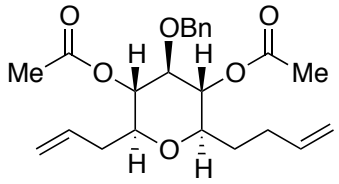
Preparation of diol 1.84. To a solution of triol **1.82** (0.11 g, 0.38 mmol) and 2,6-lutidine (0.18 mL, 1.5 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added trifluoromethanesulfonic anhydride (0.067 mL, 0.40 mmol). After 30 min, TESOTf (0.19 mL, 0.83 mmol) was added. The reaction mixture was then slowly warmed to rt and the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted

with CH_2Cl_2 (3 x 10 mL), the extracts were combined, dried (Na_2SO_4), and concentrated. The resulting residue was passed through a plug of silica gel using 10:1 hexanes:ethyl acetate and concentrated. The resulting colorless oil **1.83** was used directly in the next reaction without additional purification.

To a solution of allylmagnesium chloride (1.1 mL, 2.2 mmol) in THF (8 mL) at -78 °C was added copper(I) iodide (0.232 g, 1.10 mmol). The acetone-dry ice bath was then changed to an acetonitrile-dry ice bath. The reaction mixture was slowly warmed to 0 °C and then cooled back to -40 °C. A solution of **1.83** (0.14 g, 0.22 mmol) in THF (3 mL) was cannulated into the reaction mixture and then the reaction mixture was warmed to rt after which the reaction was quenched with sat. NH_4Cl (aq., 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to give a pale yellow oil. The oil was taken into the next step without additional purification.

To a solution of the oil from above in methanol (10 mL) was added CSA (51 mg, 0.22 mmol). The reaction mixture was stirred for 2 h at rt before the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the organic extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) provided 58 mg of **1.84** (85%, 3 steps) as a colorless oil. R_f 0.30 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D = +5.2^o$ (c = 1.38, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.30 (d, *J* = 7.3 Hz, 2H), 7.15 (t, *J* = 7.3 Hz, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 5.97 (dddd, *J* = 17.1, 10.3, 6.9, 6.9 Hz, 1H), 5.78 (dddd, *J* = 17.1, 10.2, 6.9, 6.9 Hz, 1H), 5.10 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.03 (dd, *J* = 10.3, 1.0 Hz, 1H), 4.95 (dd, *J* = 10.3, 1.0 Hz, 1H), 4.76 (s, 2 H), 3.30-

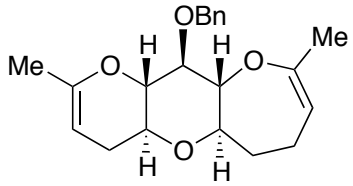
3.16 (m, 3H), 3.12-3.02 (m, 2H), 2.56 (ddd, *J* = 14.0, 6.0, 1.4 Hz, 1H), 2.36-2.10 (m, 5H), 1.94-1.86 (m, 1H), 1.48 (dddd, *J* = 14.1, 9.2, 9.2, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.4, 138.7, 135.2, 128.7, 127.9, 116.8, 114.8, 87.0, 78.9, 78.6, 74.6, 74.2, 36.4, 31.3, 29.9; IR (neat) 3428, 3075, 2917, 1641, 1497, 1453, 1361, 1090, 1001, 913 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{19}H_{26}O_4Na$ 341.2 ($M+Na^+$), found 341.1.



1.85

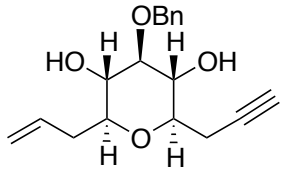
Preparation of diacetate 1.85. To a solution of **1.84** (22.4 mg, 0.0700 mmol) in CH_2Cl_2 (5 mL) was added triethylamine (0.20 mL, 1.4 mmol) and acetic anhydride (0.067 mL, 0.70 mmol). The reaction mixture was stirred for 2 h before the reaction was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (8:1 hexanes:ethyl acetate) provided 27 mg **1.85** (95%) as a colorless oil. R_f 0.65 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -4.2° (c = 1.07, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 5.83 (partially obscured dddd, *J* = 17.1, 10.3, 6.9, 6.9 Hz, 1H), 5.77 (partially obscured dddd, *J* = 17.1, 10.2, 7.3, 5.8 Hz, 1 H), 5.07 (dd, *J* = 17.6, 1.4 Hz, 1 H), 5.06 (dd, *J* = 8.3, 1.5 Hz, 1 H), 5.01 (dd, *J* = 17.1, 1.5 Hz, 1 H), 4.96 (dd, *J* = 9.7, 0.9 Hz, 1 H), 4.92 (dd, *J* = 9.8, 9.8 Hz, 1H), 4.90 (dd, *J* = 9.8, 9.8 Hz, 1H), 4.59 (s, 2H), 3.62 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.31 (ddd, *J* = 9.8, 7.8, 4.9 Hz, 1H), 3.26 (ddd, *J* = 9.8, 7.8, 4.4 Hz, 1H), 2.30-2.18 (m, 3H), 2.09 (dddd, *J* = 15.7, 7.8, 7.8, 7.8 Hz, 1H), 1.98 (s, 3H), 1.97 (s, 3H), 1.55-1.49 (m, 2H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 169.9, 169.8, 138.4, 138.2, 134.1, 128.6, 127.9, 117.3, 115.3, 82.2, 77.6, 77.0, 74.0, 36.3, 30.9, 29.5, 21.2; IR (neat) 3078, 2922, 2855, 1747, 1642, 1432, 1376, 1218, 1119, 1089, 1068 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{23}H_{31}O_6$ 403.2 ($M+H^+$), found 403.1.



1.86

Preparation of tricycle 1.86. The general two-directional olefinic ester cyclization protocol was carried out on diester **1.85** (45 mg, 0.11 mmol) to give 25 mg **1.86** (64%) as a colorless oil. R_f 0.55 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +68.4° (c = 1.44, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.52 (d, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 7.8 Hz, 1H), 5.02 (s, 2H), 4.64 (dd, *J* = 5.9, 5.9 Hz, 1H), 4.21 (broad d, *J* = 4.9 Hz, 1H), 3.66-3.62 (m, 2H), 3.52-3.47 (m, 1H), 3.30-3.22 (m, 2H), 2.17 (dddd, *J* = 15.6, 5.6, 5.6, 1.5 Hz, 1H), 2.10-2.02 (m, 1H), 2.01-1.95 (m, 1 H), 1.86 (q, *J* = 5.9 Hz, 2H), 1.70 (s, 3H), 1.62 (d, *J* = 1.0 Hz, 3H), 1.48-1.40 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 157.1, 150.6, 139.9, 128.2, 127.9, 127.4, 108.3, 93.6, 83.9, 81.6, 80.0, 79.5, 75.0, 72.2, 32.6, 27.8, 21.0, 20.8, 19.3; IR (neat) 3062, 2922, 2855, 1679, 1453, 1380, 1309, 1186, 1127, 1057, 1028 cm^{-1}; EI/MS (*m/z*) calcd for $C_{21}H_{26}O_4$ 342.2 (M^+), found 342.2.

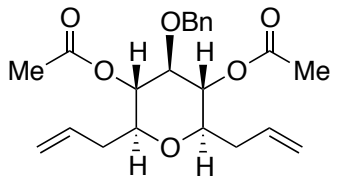


1.87

Preparation of diol 1.87. To a solution of trimethylsilylacetylene (0.11 mL, 0.76 mmol) in THF (5 mL) at 0 °C was added *n*BuLi (0.31 mL of 2.5 M solution in

hexanes, 0.76 mmol). The reaction mixture was stirred at 0 °C for 30 min and then cooled to -78 °C. To this solution was added a solution of **1.83** (0.10 g, 0.15 mmol) and HMPA (0.13 mL, 0.76 mmol) in THF (2 mL). The reaction mixture was slowly warmed to rt over 2 h before the reaction was quenched with sat. NH_4Cl (aq., 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was taken directly into the next step without additional purification.

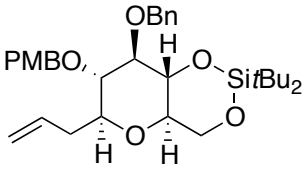
To a solution of the residue from above in methanol (20 mL) at rt was added CSA (40 mg, 0.15 mmol). After the reaction mixture had stirred for 1 h the reaction was quenched with potassium carbonate (60 mg, 0.46 mmol) and the resulting mixture was stirred for another 12 h at rt. Concentration and flash chromatography (3:2 hexanes:ethyl acetate) provided 41 mg **1.87** as a colorless oil (90%, 3 steps). R_f 0.55 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +0.7° (*c* = 0.79, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 5.93 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1H), 5.13 (dd, *J* = 17.1 Hz, 1.5 Hz, 1H), 5.07 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.87 (d, *J* = 11.7 Hz, 1H), 4.85 (d, *J* = 11.7 Hz, 1 H), 3.53 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.40-3.24 (m, 4H), 2.63 (ddd, *J* = 17.1, 3.9, 2.4 Hz, 1H), 2.57-2.48 (m, 3H), 2.40 (broad s, 1H), 2.28 (ddd, *J* = 15.1, 6.8, 6.8 Hz, 1H), 2.08 (dd, *J* = 2.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 134.7, 129.0, 128.3, 128.2, 117.4, 86.5, 80.7, 78.9, 77.0, 75.2, 73.7, 73.5, 70.6, 36.2, 22.3; IR (neat) 3296 (broad), 3072, 3007, 2858, 1618, 1455, 1420, 1361, 1250, 1091, 1009, 876 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{18}H_{23}O_4$ 303.2 ($M+H^+$), found 303.0.



1.89

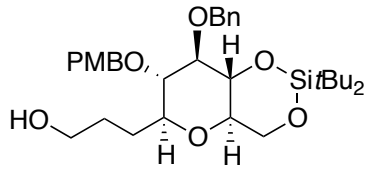
Preparation of diacetate 1.89. To a solution of **1.87** (65 mg, 0.22 mmol) in ethyl acetate (5 mL) was added quinoline (13 μL, 0.11 mmol,) and Lindlar's Pd catalyst (10 mg). The reaction mixture was stirred under a balloon of H_2 (1 atm) for 2 h before it was passed through a celite plug using ethyl acetate. The filtrate was concentrated to give a colorless oil which was taken to the next step without additional purification.

To a solution of the diol from above in CH_2Cl_2 (5 mL) was added triethylamine (0.60 mL, 4.3 mmol) and acetic anhydride (0.20 mL, 2.2 mmol). The reaction mixture was stirred for 2 h before the reaction was quenched with sat. $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the organic extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (8:1 hexanes:ethyl acetate) provided 70 mg **1.89** (84%, 2 steps) as a colorless oil. R_f 0.60 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.20 (m, 5H), 5.81 (dddd, *J* = 17.1, 10.2, 6.4, 6.4 Hz, 2H), 5.05 (partially obscured dd, *J* = 17.8, 1.4 Hz, 2H), 5.04 (partially obscured dd, *J* = 9.8, 1.0 Hz, 2 H), 4.92 (dd, *J* = 9.3, 9.3 Hz, 2H), 4.59 (s, 2H), 3.63 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.34 (ddd, *J* = 9.8, 7.3, 4.9 Hz, 2H), 2.26-2.20 (m, 4H), 1.96 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 138.4, 134.0, 128.6, 127.9, 117.4, 82.2, 77.6, 74.0, 73.7, 36.3, 21.2; IR (neat) 3087, 2959, 2859, 1747, 1646, 1432, 1226, 1120, 1066 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{22}H_{29}O_6$ 389.2 ($M+H^+$), found 389.0.



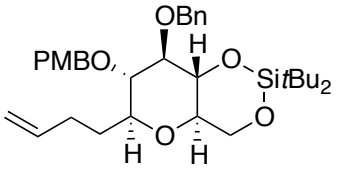
1.90

Preparation of PMB ether 1.90. To a solution of **1.81** (0.27 g, 0.62 mmol) in THF (15 mL) was added *t*BuOK (0.93 mL of 1.0 M solution in THF, 0.93 mmol). The reaction mixture was stirred for 0.5 h at rt and then cooled to 0 °C. After the slow addition of PMBBr (0.18 mL, 1.2 mmol), the reaction mixture was warmed to rt and stirred for 2 h after which the reaction was quenched with sat. NH_4Cl (aq., 15 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) afforded 0.33 g **1.90** (97%) as a colorless oil. R_f 0.60 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -10.0° (c =1.25, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 6.8 Hz, 2H), 7.39 (dt, *J* = 6.8, 2.0 Hz, 2H), 7.36-7.32 (m, 1H), 7.28 (d, *J* = 8.8 Hz, 2H), 6.95-6.91 (m, 2H), 5.90 (dddd, *J* =17.1, 10.3, 7.3, 7.3 Hz, 1H), 5.16 (d, *J* = 9.7 Hz, 1 H), 5.12-5.10 (m, 2H), 4.93 (d, *J* = 10.7 Hz, 1H), 4.89 (d, *J* = 10.7 Hz, 1H), 4.62 (d, *J* = 10.7 Hz, 1H), 4.24 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.97 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.90 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.83 (s, 3H), 3.68 (dd, *J* = 8.3 Hz, 1H), 3.48-3.42 (m, 2H), 3.33 (dd, *J* = 9.3, 9.3 Hz, 1H), 2.65-2.60 (m, 1H), 2.28 (ddd, *J* = 14.6, 7.3, 7.3 Hz, 1H), 1.16 (s, 9H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 139.2, 134.8, 129.9, 128.7, 128.5, 128.0, 117.5, 114.1, 87.0, 80.4, 79.3, 79.1, 75.7, 75.1, 74.7, 66.9, 55.5, 36.3, 28.0, 27.8, 27.4, 23.0, 20.2; IR (neat) 2935, 2887, 2860, 1613, 1514, 1469, 1390, 1301, 1249, 1167, 1094 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{32}H_{46}O_6Si$ (M^+) , found , 577.2 $(M+Na)^+$.



1.91

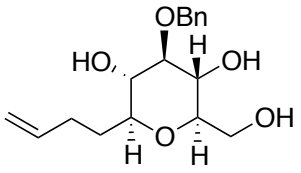
Preparation of alcohol 1.91. To a solution of **1.90** (0.33 g, 0.62 mmol) in THF (5 mL) at 0 °C was added BH_3•DMS (1.2 mL of 2.0 M solution in THF, 2.5 mmol). The reaction mixture was stirred for 2 h at 0 °C before the reaction was quenched with H_2O (0.1 mL). To the resulting mixture was added NaOH (3.6 mL of 3.0 M aq. solution, 11 mmol) followed by H_2O_2 (13 mL of 30% aq. solution). The reaction mixture was then allowed to warm to rt and stirred overnight. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) gave 0.31 g **1.91** (90%) as a colorless oil. R_f 0.45 (2:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -13.9°(c = 1.31, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 6.8 Hz, 2H), 7.36 (t, *J* = 6.8 Hz, 2H), 7.32-7.28 (m, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 6.3 Hz, 2H), 5.11 (d, *J* =10.7 Hz, 1H), 4.89 (d, *J* = 10.3 Hz, 1H), 4.85 (d, *J* = 10.3 Hz, 1H), 4.58 (d, *J* = 10.7 Hz, 1H), 4.18 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.94 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.86 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.80 (s, 3H), 3.63 (dd, *J* = 8.3, 8.3 Hz, 1H), 3.57 (broad t, *J* = 6.4 Hz, 2H), 3.40 (ddd, *J* = 9.8, 9.8, 4.9 Hz, 1H), 3.34 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.23 (dd, *J* = 9.3 Hz, 1H), 2.33 (s, 1H), 1.93 (ddd, *J* = 14.2, 7.3, 7.3 Hz, 1H), 1.71-1.57 (m, 2H), 1.48-1.38 (m, 1H), 1.12 (s, 9H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 139.1, 130.7, 130.0, 128.7, 128.5, 128.0, 114.1, 86.8, 80.9, 79.7, 79.0, 75.7, 75.3, 74.6, 66.8, 62.8, 55.5, 28.9, 28.5, 27.8, 27.3, 22.9, 20.2; IR (neat) 3384, 2934, 2860, 1613, 1514, 1469, 1363, 1302, 1249, 1164, 1100, 826 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{32}H_{48}O_7SiNa$ 595.3 ($M+Na^+$), found 595.3.



1.92

Preparation of alkene 1.92. To a solution of **1.91** (0.214 g, 0.374 mmol) in CH_2Cl_2 (10 mL) was added 4Å MS (0.25 g), NMO (0.18 g, 1.5 mmol), and TPAP (5.0 mg, 0.014 mmol). The reaction mixture was stirred at rt for 2 h before it was transferred into a flask containing freshly prepared triphenylphosphonium methylide (6.0 mL of 0.19 M solution in THF, 1.1 mmol) via cannula. The reaction mixture was then stirred for 2 h before the reaction was quenched with sat. NH_4Cl (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (20:1 hexanes:ethyl acetate) gave 0.13 g **1.92** (62%) as a colorless oil. R_f 0.45 (10:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -13.6° (c = 0.73, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 6.8 Hz, 2H), 7.38 (t, *J* = 6.8 Hz, 2H), 7.34-7.32 (m, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 6.3 Hz, 2H), 5.83 (dddd, *J* =17.1, 10.2, 6.8, 6.8 Hz, 1H), 5.13 (d, *J* = 11.2 Hz, 1H), 5.04 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.99 (d, *J* = 10.2, 1.5 Hz, 1H), 4.90 (d, *J* = 10.7 Hz, 1H), 4.87 (d, *J* = 10.7 Hz, 1H), 4.60 (d, *J* = 10.7 Hz, 1H), 4.20 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.95 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.88 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.83 (s, 3H), 3.65 (dd, *J* = 8.3, 8.3 Hz, 1H), 3.39 (partially obscured ddd, *J* = 9.8, 9.8, 4.9 Hz, 1H), 3.35 (partially obscured ddd, *J* = 9.3, 9.3, 2.4 Hz, 1H), 3.25 (dd, *J* = 9.3, 9.3 Hz, 1H), 2.28-2.21 (m, 1H), 2.12 (dddd, *J* = 15.2, 7.4, 7.4, 7.4 Hz, 1H), 1.97-1.90 (m, 1H), 1.48 (dddd, *J* = 14.2, 9.3, 9.3, 4.9 Hz, 1H), 1.14 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 139.2, 138.6, 130.8, 129.9, 128.7, 128.5, 127.9, 115.0, 114.1, 87.0, 81.1, 79.2, 79.1, 75.7, 75.3, 74.6, 66.9, 55.5, 31.4, 29.7, 27.8, 27.4,

23.0, 20.2; IR (neat) 2933, 2859, 1613, 1514, 1468, 1249, 1094 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{33}H_{48}O_6SiNa$ 591.3 ($M+Na^+$), found 591.1.

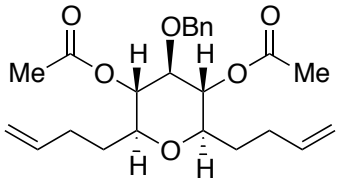


1.93

Preparation of triol 1.93. To a solution of **1.92** (0.132 g, 0.232 mmol) in 9:1 CH_2Cl_2:H_2O (10 mL) was added DDQ (74.0 mg, 0.325 mmol). The reaction mixture was stirred for 2 h before the reaction was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to give a brown oil which was taken into the next step without additional purification.

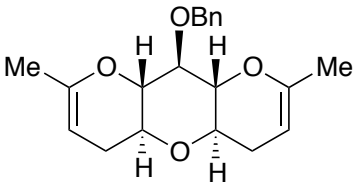
To a solution of the brown oil from above in THF (10 mL) at 0 °C was added HF•Py (0.46 mL of 1.0 M solution in THF, 0.46 mmol). The reaction mixture was stirred for 2 h before the reaction was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate) gave 71 mg **1.93** (100%, 2 steps) as a colorless oil. R_f 0.15 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +2.9° (c = 0.28, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 5.80 (dddd, *J* =17.0, 9.7, 6.8, 6.8 Hz, 1H), 5.02 (d, *J* = 17.0 Hz, 1H), 4.96 (d, *J* = 9.7 Hz, 1H), 4.91 (d, *J* = 12.2 Hz, 1H), 4.82 (d, *J* = 12.2 Hz, 1H), 3.80 (dd, *J* = 11.7, 3.0 Hz, 1H), 3.72 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.59 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.34 (dd, *J* = 8.3, 8.3 Hz, 1H), 3.28-3.19 (m, 4H), 2.60 (broad s, 2H), 2.29-2.22 (m, 1H), 2.10 (dddd, *J* = 15.1, 7.3, 7.3, 7.3 Hz, 1H), 1.90 (ddd, *J* = 14.1, 7.3, 7.3 Hz, 1H), 1.48 (dddd, *J* = 14.2, 8.8, 8.8, 5.4 Hz,

1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 138.6, 129.0, 128.3, 128.1, 115.0, 86.8, 79.1, 78.9, 75.1, 74.0, 71.1, 62.7, 31.1, 29.7; IR (neat) 3388 (broad), 2921, 2857, 1641, 1497, 1362, 1248, 1092, 1027 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{17}H_{25}O_5$ 309.2 ($M+H^+$), found 309.1.



1.95

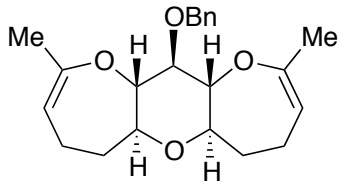
Preparation of diacetate 1.95. Prepared from **1.93** (62.1 mg, 0.202 mmol) according to the same procedure used for the preparation of **1.85** (53%, 4 steps). R_f 0.70 (3:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (t, *J* = 6.8 Hz, 2 H), 7.28-7.25 (m, 1 H), 7.23 (d, *J* = 6.9 Hz, 2H), 5.77 (dddd, *J* = 17.1, 10.3, 7.3, 6.3 Hz, 2H), 5.02 (dd, *J* = 17.1, 1.5 Hz, 2H), 4.97 (d, *J* = 10.2 Hz, 2H), 4.89 (dd, *J* = 9.3, 9.3 Hz, 2H), 4.59 (s, 2H), 3.62 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.25 (ddd, *J* = 9.8, 7.8, 4.4 Hz, 2H), 2.29 (dddd, *J* = 14.2, 6.4, 6.4, 6.4 Hz, 2H), 2.10 (dddd, *J* = 15.2, 7.8, 7.8, 7.8 Hz, 2H), 1.98 (s, 6H), 1.55-1.50 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 138.2, 128.6, 127.9, 115.3, 82.2, 77.0, 74.1, 31.0, 29.6, 21.2; IR (neat) 3074, 2951, 2851, 1749, 1452, 1377, 1212, 1092, 1071, 1032 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{24}H_{33}O_6$ 417.2 ($M+H^+$), found 417.1.



1.96

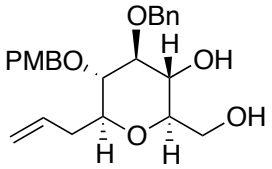
Preparation of tricycle 1.96. The general two-directional olefinic ester cyclization reaction protocol was carried out on diester **1.89** (65.6 mg, 0.169 mmol) to

give 36.0 mg **1.96** (65%) as a colorless oil. R_f 0.45 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 6.9 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.4 Hz, 1H), 4.92 (s, 2H), 4.44 (broad d, *J* = 4.9 Hz, 2H), 3.68 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.62 (dd, *J* = 9.8, 9.8 Hz, 2H), 3.52 (ddd, *J* = 9.3, 9.3, 6.4 Hz, 2H), 2.28 (dddd, *J* = 16.1, 6.8, 6.8, 1.5 Hz, 2H), 2.11-2.04 (m, 2H), 1.79 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 139.2, 128.4, 128.2, 127.7, 93.5, 80.7, 78.8, 74.7, 72.6, 27.6, 19.5; IR (neat) 3052, 2889, 1676, 1499, 1443, 1376, 1304, 1181, 1092, 1042, 972, 912 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{20}H_{25}O_4$ 329.2 ($M+H^+$), found 329.0.



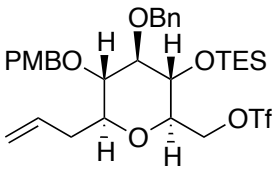
1.97

Preparation of tricycle 1.97. The general two-directional olefinic ester cyclization reaction protocol was carried out on diester **1.95** (52 mg, 0.13 mmol) to give 29 mg **1.97** (65%) as a colorless oil. R_f 0.60 (5:1 hexanes:ethyl acetate); ^{1}H NMR (500 MHz, C_6D_6) δ 7.52 (dd, *J* = 7.3, 1.5 Hz, 2H), 7.20 (dt, *J* = 7.3, 1.9 Hz, 2H), 7.10 (partially obscured t, *J* = 7.3 Hz, 1H), 5.02 (s, 2H), 4.65 (ddd, *J* = 6.1, 6.1, 0.9 Hz, 2H), 3.62 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.43 (dd, *J* = 9.3, 9.3 Hz, 2H), 3.23 (ddd, *J* = 9.3, 7.8, 4.4 Hz, 2H), 2.22-1.96 (m, 2H), 1.89-1.82 (m, 4H), 1.70 (s, 6H), 1.44 (dddd, *J* = 13.7, 9.8, 8.3, 4.4 Hz, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 157.0, 139.9, 128.3, 128.0, 127.4, 108.3, 84.2, 82.4, 79.8, 75.7, 32.7, 21.0, 20.8; IR (neat) 3031, 2926, 2893, 2851, 1681, 1430, 1376, 1309, 1277, 1170, 1088, 1053 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{22}H_{28}O_4Na$ 379.2 ($M+Na^+$), found 379.1.



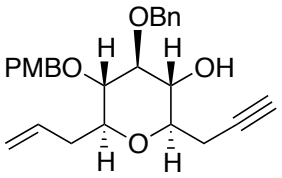
1.98

Preparation of diol 1.98. To a solution of **1.90** (0.186 g, 0.336 mmol) in THF (10 mL) at 0 °C was added a solution of HF•Py (0.67 mL of 1.0 M solution in THF, 0.67 mmol) dropwise. After stirring for 2 h, the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL), and the organic extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (2:1 to 1:1 hexanes:ethyl acetate) provided 0.117 g of diol **1.98** (85%) as a colorless oil. R_f 0.20 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +24.7° (c = 0.49, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.30 (m, 5H), 7.26 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 5.90 (dddd, *J* = 17.1, 10.3, 7.3, 7.3 Hz, 1H), 5.14 (d, *J* = 17.1 Hz, 1H), 5.10 (d, *J* = 10.3 Hz, 1H), 4.96 (d, *J* = 11.7 Hz, 1H), 4.86 (d, *J* = 11.7 Hz, 1H), 4.83 (d, *J* = 10.3 Hz, 1H), 4.60 (d, *J* = 10.3 Hz, 1H), 3.85-3.80 (partially obscured m, 1 H), 3.82 (s, 3 H), 3.72 (broad dd, *J* = 11.7, 4.4 Hz, 1H), 3.57 (broad dd, *J* = 9.3, 9.3 Hz, 1H), 3.54 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.40 (ddd, *J* = 9.8, 7.8, 2.9 Hz, 1H), 3.30-3.24 (m, 2H), 3.13 (broad s, 1H), 2.66-2.58 (m, 2H), 2.28 (ddd, *J* = 15.1, 7.3, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 138.9, 134.9, 130.5, 129.9, 128.9, 128.1, 128.0, 117.5, 114.2, 87.0, 81.4, 79.1, 78.8, 75.5, 75.0, 71.3, 62.8, 55.5, 36.2; IR (neat) 3318 (broad), 2930, 1613, 1514, 1456, 1359, 1303, 1248, 1093, 1037 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{24}H_{30}O_6Na$ 437.2 ($M+Na^+$), found 437.2.



1.99

Preparation of triflate 1.99. To a solution of diol **1.98** (0.116 g, 0.280 mmol) and 2,6-lutidine (0.13 mL, 1.1 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added trifluoromethanesulfonic anhydride (0.050 mL, 0.29 mmol). TESOTf (0.082 mL, 0.36 mmol) was added after 30 min, and the resulting mixture was slowly warmed to rt before the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) gave 0.154 g **1.99** (83%) as a colorless oil. R_f 0.40 (10:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +36.5° (c = 0.53, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.30 (d, *J* = 7.3 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 2H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 5.98 (dddd, *J* = 17.1, 10.3, 7.3, 7.3 Hz, 1H), 5.08 (d, *J* = 17.1 Hz, 1H), 5.05 (d, *J* = 10.3 Hz, 1H), 5.00 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 10.3 Hz, 2H), 4.37-4.33 (m, 2H), 3.56 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.28-3.21 (m, 4H), 3.17 (ddd, *J* = 12.2, 7.3, 2.9 Hz, 1H), 3.10 (dd, *J* = 10.3, 10.3 Hz, 1H), 2.96 (ddd, *J* = 9.2, 4.3, 1.9 Hz, 1H), 2.54-2.48 (m, 1H), 2.20 (ddd, *J* = 14.7, 7.3, 7.3 Hz, 1H), 0.86 (t, *J* = 7.8 Hz, 9H), 0.60-0.49 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.7, 139.2, 134.3, 130.5, 129.4, 128.4, 127.3, 126.4, 119.2 (q, *J* = 325 Hz), 117.5, 113.9, 86.6, 81.8, 79.0, 77.3, 75.1, 74.8, 74.7, 70.6, 54.6, 36.0, 6.9, 5.2; IR (neat) 2957, 2879, 1613, 1515, 1459, 1415, 1302, 1248, 1145, 1114 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{31}H_{43}F_3O_8SSiNa$ 683.2 ($M+Na^+$), found 683.1.

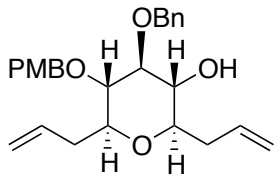


1.100

Preparation of alkyne 1.100. To a solution of trimethylsilylacetylene (1.37 mL, 9.75 mmol) in THF (20 mL) at 0 °C was added *n*BuLi (3.9 mL of 2.5 M solution in hexanes, 9.8 mmol). After 30 min, the reaction mixture was cooled to -78 °C and to this was transferred a solution of **1.99** (1.29 g, 1.95 mmol) and HMPA (1.68 mL, 9.75 mmol) in THF (5 mL). The reaction mixture was slowly warmed to rt over 2 h before the reaction was quenched with sat. NH_4Cl (aq., 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the organic extracts were combined, dried (Na_2SO_4), and concentrated to give a dark brown syrup that was taken directly into the next step without additional purification.

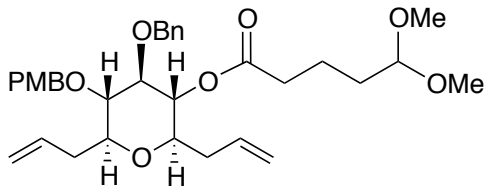
To a solution of the residue from above in methanol (30 mL) was added CSA (0.87 g, 3.9 mmol). After 1 h, the reaction was quenched with potassium carbonate (1.08 g, 7.80 mmol). The resulting mixture was stirred for another 12 h and then concentrated. Flash chromatography (6:1 hexanes:ethyl acetate) provided 0.72 g **1.100** (88%, 3 steps) as a colorless oil. R_f 0.40 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +16.1° (*c* = 0.79, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.38 (m, 5H), 7.34 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.09 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.26 (d, *J* = 17.1 Hz, 1H), 5.23 (d, *J* = 10.2 Hz, 1H), 5.07 (d, *J* = 11.3 Hz, 1H), 4.93 (d, *J* = 11.3 Hz, 1H), 4.89 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 3.84 (s, 3H), 3.61 (p, *J* = 8.8 Hz, 2H), 3.49-3.44 (m, 1H), 3.43-3.36 (m, 2H), 2.87 (s, 1H), 2.77-2.67 (m, 2H), 2.60 (ddd, *J* = 17.1, 6.4, 2.4 Hz, 1H), 2.43 (dt, *J* = 14.6, 7.3 Hz, 1H), 2.14 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ

159.7, 139.1, 135.1, 130.7, 129.9, 129.0, 128.7, 128.1, 117.4, 114.3, 87.0, 81.5, 81.0, 79.0, 77.1, 75.5, 75.0, 73.6, 70.7, 55.5, 36.1, 22.4; IR (neat) 3449, 3291, 3070, 2907, 1641, 1514, 1457, 1422, 1360, 1249, 1090, 1034, 821 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{26}H_{30}O_5Na$ 445.2 ($M+Na^+$), found 445.1.



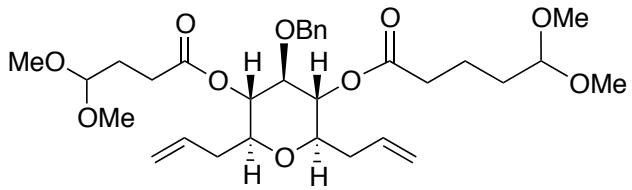
1.101

Preparation of alcohol 1.101. To a solution of **1.100** (0.50 g, 1.2 mmol) in ethyl acetate (20 mL) was added quinoline (0.070 mL, 0.59 mmol,) and Lindlar's Pd catalyst (50 mg). The reaction mixture was stirred under a balloon of H_2 (1 atm) for 2 h before it was passed through a celite plug using ethyl acetate. The filtrate was concentrated and flash chromatography (5:1 hexanes:ethyl acetate) gave 0.48 g **1.101** (95%) as a white solid. R_f 0.40 (3:1 hexanes:ethyl acetate); m.p. 70-72 °C; $[\alpha]^{20}_D$ = +22.1° (*c* = 0.67, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.43-7.31 (m, 5H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.98-5.87 (m, 2H), 5.15-5.06 (m, 4H), 5.00 (d, *J* = 11.7 Hz, 1H), 4.81 (d, *J* = 10.2 Hz, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 10.2 Hz, 1H), 3.81 (s, 3H), 3.48 (t, *J* = 8.8 Hz, 1H), 3.38-3.25 (m, 3H), 3.22 (td, *J* = 8.3, 3.4 Hz, 1H), 2.63-2.53 (m, 2H), 2.31-2.21 (m, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.6, 139.4, 135.2, 135.1, 131.0, 129.5, 128.6, 127.7, 116.9, 113.9, 87.3, 81.7, 78.9, 78.8, 75.0, 74.5, 74.2, 54.7, 36.4, 36.3; IR (neat) 3420, 3073, 2904, 1641, 1514, 1458, 1433, 1361, 1249, 1090, 1034, 821 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{26}H_{32}O_5Na$ 447.2 ($M+Na^+$), found 447.2.



1.103

Preparation of ester 1.103. To a solution of **1.101** (0.10 g, 0.24 mmol) in CH_2Cl_2 (10 mL) was added 5,5-dimethoxypentanoic acid (**1.102**[56], 57 mg, 0.35 mmol), DCC (0.10 g, 0.47 mmol) and DMAP (29 mg, 0.24 mmol). The reaction mixture was stirred at rt for 2 h before the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL), the extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (3:1, hexanes:ethyl acetate) provided 0.131 g **1.103** (98%) as a colorless oil. R_f 0.40 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +14.9° (c = 1.16, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.25 (m, 5H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.95-5.78 (m, 2H), 5.13-5.02 (m, 4H), 4.91 (t, *J* = 9.3 Hz, 1H), 4.84 (d, *J* = 11.2 Hz, 1H), 4.76 (d, *J* = 10.7 Hz, 1H), 4.67 (d, *J* = 11.2 Hz, 1H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.32 (t, *J* = 4.9 Hz, 1H), 3.78 (s, 3H), 3.62 (t, *J* = 8.3 Hz, 1H), 3.38-3.26 (m, 9H), 2.58 (dd, *J* = 13.5, 5.4 Hz, 1H), 2.30-2.12 (m, 5H), 1.68-1.56 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 159.6, 138.7, 134.8, 134.2, 130.4, 129.9, 128.6, 127.8, 117.3, 114.1, 104.4, 85.0, 81.6, 78.8, 77.4, 75.3, 75.0, 74.1, 55.5, 53.0, 36.4, 36.1, 34.1, 32.1, 20.1; IR (neat) 3074, 2951, 2858, 1740, 1643, 1586, 1459, 1362, 1249, 1125, 1081, 917 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{33}H_{44}O_8Na$ 591.3 ($M+Na^+$), found 591.1.

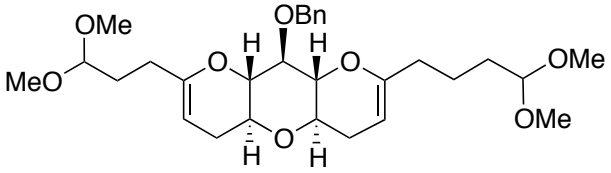


1.105

Preparation of diester 1.105. To a mixture of **1.103** (49 mg, 0.086 mmol) in CH_2Cl_2 (9 mL) and pH 7 phosphate buffer (1 mL) was added DDQ (22 mg, 0.095 mmol). The reaction mixture was stirred for 12 h before the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided 38 mg the free alcohol (99%) as a colorless oil. R_f 0.35 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -12.1° (c = 0.43, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.33 (d, *J* = 7.8 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 2H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.02 (dddd, *J* = 17.2, 10.3, 7.3, 7.3 Hz, 1H), 5.96 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.19-5.04 (m, 5H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.19 (t, *J* = 5.9 Hz, 1H), 3.41 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.33 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.23 (ddd, *J* = 9.8, 6.8, 4.4 Hz, 1H), 3.17 (ddd, *J* = 9.3, 7.8, 3.4 Hz, 1H), 3.09 (s, 3H), 3.08 (s, 3H), 2.61 (m, 1H), 2.36-2.24 (m, 4H), 2.08 (ddd, *J* = 7.3, 7.3, 3.9 Hz, 2H), 1.68-1.61 (m, 2H), 1.58-1.53 (m, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.0, 139.1, 134.9, 134.3, 128.6, 127.7, 127.6, 117.1, 117.0, 114.2, 84.7, 79.1, 77.4, 74.2, 73.7, 73.6, 52.2, 36.5, 36.3, 33.9, 31.9, 20.2; IR (neat) 3449, 3076, 2949, 1743, 1643, 1456, 1364, 1127, 1092, 916 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{25}H_{36}O_7Na$ 471.3 ($M+Na^+$), found 471.1.

To a solution of the alcohol from above (82 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) was added 4, 4-dimethoxybutanoic acid (**1.104**[57], 54 mg, 0.36 mmol), DCC (0.15 g, 0.73 mmol) and DMAP (44 mg, 0.36 mmol). The reaction mixture was stirred at rt for 2 h before the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL) and the extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) provided 84 mg

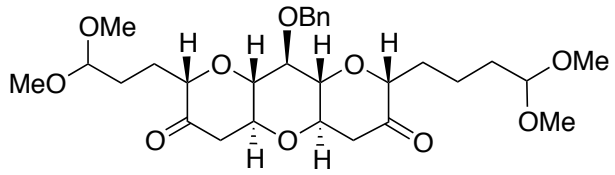
1.105 (80%) as a colorless oil. R_f 0.33 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +1.1° (c = 0.66, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.28 (d, *J* = 7.3 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 2H), 7.02 (dt, *J* = 7.3, 2.0 Hz, 1H), 5.86 (dddd, *J* = 17.1, 10.2, 6.3, 6.3 Hz, 2H), 5.15 (dd, *J* = 9.6, 9.6 Hz, 1H), 5.14 (dd, *J* = 9.6, 9.6 Hz, 1H), 5.05 (d, *J* = 17.1 Hz, 2H), 5.01 (d, *J* = 10.2 Hz, 2H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.19 (dd, *J* = 5.6, 5.6 Hz, 1H), 4.14 (dd, *J* = 5.6, 5.6 Hz, 1H), 3.56 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.18-3.14 (m, 2H), 3.05 (s, 3H), 3.04 (s, 3H), 3.01 (s, 3H), 3.00 (s, 3H), 2.32-2.18 (m, 6H), 2.08-1.98 (m, 2H), 1.92-1.81 (m, 2H), 1.64-1.48 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 171.6, 138.8, 134.2, 134.1, 128.4, 127.5, 127.5, 117.2, 117.1, 104.2, 103.5, 82.2, 77.6, 73.3, 73.1, 73.0, 52.7, 52.6, 52.2, 36.4, 36.3, 33.9, 31.9, 29.2, 27.8, 20.2; IR (neat) 3073, 2937, 2832, 1745, 1646, 1435, 1367, 1156, 1126, 1084 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{31}H_{46}O_{10}Na$ 601.3 ($M+Na^+$), found 601.1.



1.106

Preparation of tricycle 1.106. The general two-directional olefinic ester cyclization reaction protocol was carried out on diester **1.105** (77 mg, 0.13 mmol) to give 41 mg **1.106** (60%) as a colorless oil. R_f 0.45 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = 0° (c = 0.51, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.57 (d, *J* = 7.8 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 2H), 7.13-7.10 (m, 1H), 5.04 (d, *J* = 12.2 Hz, 1H), 5.01 (d, *J* = 12.2 Hz, 1H), 4.33 (dd, *J* = 5.9, 5.9 Hz, 1H), 4.31-4.24 (m, 3H), 3.68-3.58 (m, 3H), 3.30-3.22 (m, 2H), 3.11 (s, 6H), 3.10 (s, 6H), 2.19-2.10 (m, 4H), 2.08-1.88 (m, 6H), 1.64-1.60 (m, 4H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.9, 153.7, 139.7, 128.3, 128.0, 127.4, 104.3, 103.9, 93.6, 93.4,

80.5, 79.3, 79.2, 74.3, 72.5, 72.4, 52.2, 52.1, 52.2, 33.4, 32.0, 30.3, 29.0, 27.7, 22.3; IR (neat) 3066, 2929, 2830, 1677, 1452, 1384, 1322, 1167, 1125, 1098 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{29}H_{42}O_8Na$ 541.3 ($M+Na^+$), found 541.1.



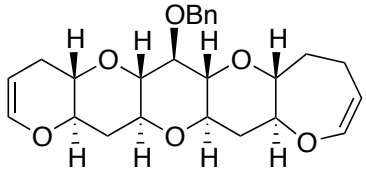
1.108

Preparation of diketone 1.108. To a solution of **1.106** (10.3 mg, 0.0200 mmol) in CH_2Cl_2 (3 mL) at -78 °C was added DMDO (0.8 mL of 0.1 M solution in acetone, 0.08 mmol) dropwise. After warming to 0 °C the reaction mixture was concentrated. To a solution of the resulting residue in THF (3 mL) at -78 °C was added *i*Bu_2AlH (0.24 mL of 1.0 M solution in hexane, 0.24 mmol). The reaction mixture was stirred for 1 h at -78 °C before the reaction was quenched with sat. NH_4Cl (aq., 10 mL). The resulting mixture was warmed to rt and the aqueous phase was extracted with ethyl acetate (3 x 10 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to give a colorless oil which was taken to the next step without additional purification.

To a solution of the residue from above in CH_2Cl_2 (5 mL) was added 4Å MS (10 mg), NMO (47 mg, 0.40 mmol) and TPAP (2 mg, 6 μmol). The reaction mixture was stirred at rt for 2 h and then concentrated. Flash chromatography (1:1 hexanes: ethyl acetate) gave 7.3 mg of diketones (67%, 2 steps) as a 1:1 mixture of diastereomers.

To a solution of the diketones obtained above (7.3 mg, 13 mmol) from above in toluene (5 mL) was added DBU (1 drop). The reaction mixture was heated at reflux for 12 h before it was cooled to rt and the reaction was quenched with sat. NH_4Cl (aq., 5

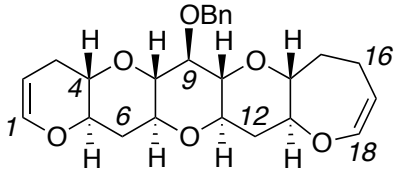
mL). The organic phase was washed with H_2O (2 x 5 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate) gave 5.5 mg (75%) of an 8:1 mixture of diketones favoring **1.108**. R_f 0.25 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D = 0^o$ (c = 0.36, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.43 (d, *J* = 7.3 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.3 Hz, 1H), 4.92 (d, *J* = 11.7 Hz, 1H), 4.88 (d, *J* = 11.7 Hz, 1H), 4.40 (t, *J* = 5.4 Hz, 1H), 4.35 (t, *J* = 5.4 Hz, 1H), 3.90 (dd, *J* = 7.8, 3.9 Hz, 1H), 3.86 (dd, *J* = 7.8, 3.4 Hz, 1H), 3.70-3.54 (m, 5H), 3.31 (s, 3H), 3.30 (s, 3H), 3.29 (s, 3H), 3.29 (s, 3H), 2.92 (dd, *J* = 15.6, 5.4 Hz, 2H), 2.51 (dd, *J* = 15.6, 11.2 Hz, 2H), 2.00-1.88 (m, 2H), 1.84-1.42 (m, 8H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 204.5, 204.3, 139.0, 128.4, 128.0, 127.8, 104.7, 104.5, 83.3, 82.9, 81.1, 81.0, 80.1, 74.8, 52.8, 52.8, 52.6, 45.0, 32.7, 29.3, 28.3, 24.7, 20.8; IR (neat) ν_{max} 2930, 1718, 1456, 1367, 1322, 1104 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{29}H_{42}O_{10}Na$ 573.3 ($M+Na^+$), found 573.2.



1.110

Preparation of pentacycle 1.110. To a solution of **1.108** (1.3 mg, 2.4 mmol) in EtOH (1 mL) at -78 °C was added $CeCl_3 \bullet 7H_2O$ (12 mg, 34 μmol) and $NaBH_4$ (2.1 mg, 58 μmol). The reaction mixture was stirred at -78 ^{o}C for 1 h before it was warmed to 0 °C and the reaction quenched with acetone (2 mL). After stirring for another 2 h, the reaction mixture was concentrated. Flash chromatography (2:1 hexanes:ethyl acetate) gave a mixture of diols as a colorless oil. The mixture was taken into the next step without further purification.

To a solution of the diols from above in chlorobenzene (3 mL) was added PPTS (9.1 mg, 36 μmol) and pyridine (4 μL, 50 μmol). The reaction mixture was heated at reflux for 12 h before it was cooled to rt and the reaction was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (5:1 hexanes: ethyl acetate) provided 0.6 mg of **1.110** (61%, 2 steps) as a colorless film. R_f 0.65 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +20.0° (c = 0.11, THF); ^{1}H NMR (500 MHz, C_7D_8) δ 7.43 (d, *J* = 7.3 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 2H), 7.08 (t, *J* = 7.3 Hz, 1H), 6.24 (dd, *J* = 6.4, 2.4 Hz, 1H), 6.15 (d, *J* = 5.9 Hz, 1H), 4.88 (s, 2H), 4.69 (ddd, *J* = 6.8, 6.8, 4.9 Hz, 1H), 4.39 (ddd, *J* = 5.9, 5.9, 2.0 Hz, 1H), 3.32 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.23 (ddd, *J* = 11.2, 9.3, 4.4 Hz, 1H), 3.20 (ddd, *J* = 11.7, 9.3, 4.9 Hz, 1H), 3.12 (ddd, *J* = 9.3, 9.3, 5.9 Hz, 1H), 3.07 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.05 (ddd, *J* = 8.8, 8.8, 3.9 Hz, 1H), 3.02 (dd, *J* = 9.3, 9.3 Hz, 1H), 2.85 (ddd, *J* = 11.2, 9.3, 3.9 Hz, 1H), 2.80 (ddd, *J* = 11.7, 9.8, 4.4 Hz, 1H), 2.36 (dd, *J* = 9.3, 4.4 Hz, 1H), 2.34 (dd, *J* = 9.7, 4.9 Hz, 1H), 2.12-2.06 (m, 1H), 2.04-1.88 (m, 2H), 1.85 (ddd, *J* = 7.3, 7.3, 3.4 Hz, 1H), 1.82-1.74 (m, 1H), 1.65 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.56 (ddd, *J* = 11.2, 11.2, 11.2 Hz, 1H), 1.43-1.34 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 147.9, 143.5, 140.0, 128.2, 128.0, 127.3, 111.7, 98.4, 82.5, 82.3, 82.1, 80.3, 78.8, 75.1, 74.8, 74.7, 74.3, 73.7, 36.9, 35.4, 32.9, 27.1, 20.9; IR (neat) 2924, 2856, 1647, 1458, 1375, 1268, 1238, 1101, 1032 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{25}H_{30}O_6Na$ 449.2 ($M+Na^+$), found 449.2.



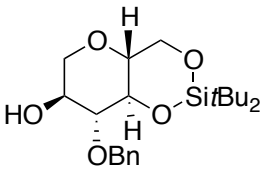
1.110

$J_{4,5}$ = 9.3 Hz

$J_{13,14}$ = 8.8 Hz

Summary of COSY spectrum for **1.110** (500 MHz, C_7D_8):

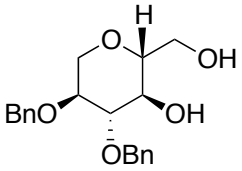
1. Proton at 6.24 ppm (C-18) showed a cross peak with the proton at 4.69 ppm (C-17).
2. Proton at 4.69 ppm (C-17) showed a cross peak with the protons at 1.78 ppm (C-16) and 1.86 ppm (C-16').
3. Proton at 1.86 ppm (C-16') showed a cross peak with the proton at 1.38 ppm (C-15).
4. Proton at 1.38 ppm (C-15) showed a cross peak with the protons at 1.96 ppm (C-15') and 3.05 (C-14).
5. Proton at 6.15 ppm (C-1) showed a cross peak with the proton at 4.39 ppm (C-2).
6. Proton at 4.39 ppm (C-2) showed a cross peak with the protons at 2.08 ppm (C-3) and 1.96 (C-3').
7. Proton at 2.08ppm (C-3) showed a cross peak with the proton at 3.12 ppm (C-4).



1.123

Preparation of alcohol 1.123. To a solution of **1.122** (0.34 g, 0.75 mmol) in CH_2Cl_2 (5 mL) at -78 °C was added DMDO (15 mL of a 0.10 M solution in CH_2Cl_2, 1.5 mmol) dropwise. The reaction mixture was warmed to 0 °C and then concentrated. To a solution of the resulting residue in CH_2Cl_2 (5 mL) at -78 °C was added *i*Bu_2AlH (4.5 mL of a 1.0 M solution in hexanes, 4.5 mmol). The reaction mixture was stirred for 2 h at -78 ^oC before the reaction was quenched with sat. NH_4Cl (aq., 10 mL). The resulting mixture was warmed to rt and sat. potassium sodium tartrate solution (aq., 20 mL) was added. After stirring for 30 min, the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (5:1

hexanes:ethyl acetate) provided 0.26 g **1.123** (73%) as a colorless oil. R_f 0.47 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -39.2° (c = 2.09, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.30 (m, 5H), 5.13 (d, *J* = 11.2 Hz, 1H), 4.76 (d, *J* = 11.2 Hz, 1H), 4.18 (dd, *J* = 10.3, 4.9 Hz, 1H), 3.97 (dd, *J* = 10.7, 5.4 Hz, 1H), 3.90 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.85 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.70-3.63 (m, 1H), 3.40-3.34 (partially obscured m, 1H), 3.36 (dd, *J* = 10.6, 10.6 Hz, 1 H), 3.25 (dd, *J* = 10.7, 10.7 Hz, 1H), 2.58 (d, *J* = 2.0 Hz, 1H), 1.08 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 128.8, 128.4, 128.2, 86.1, 78.5, 75.8, 75.2, 69.9, 69.4, 66.8, 27.7, 27.3, 22.9, 20.2; IR (neat) 3421, 2934, 2860, 1595, 1471, 1364, 1161, 1104, 1034 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{21}H_{35}O_5Si$ 395.2 ($M+H^+$), found 395.3.

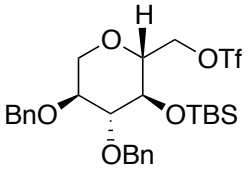


1.124

Preparation of diol 1.124. To a solution of **1.123** (0.17 g, 0.44 mmol) in THF (10 mL) at rt was added *t*BuOK (0.88 mL of 1.0 M solution in THF, 0.88 mmol). After stirring for 30 min, the reaction mixture was cooled to 0 °C and benzyl bromide (0.21 mL, 1.8 mmol) and tetrabutylammonium iodide (16 mg, 0.044 mmol) were added. The reaction mixture was slowly warmed to rt over 2 h before the reaction was quenched with sat. NH_4Cl (aq., 10 mL). The aqueous phase was extracted with ether (3 x 10 mL) and the extracts were dried (Na_2SO_4) and concentrated to give a light yellow oil which was taken to the next step without additional purification.

To a solution of the residue from above in 10 mL THF at 0 °C was added HF•Py (0.88 mL of 1.0 M solution in THF, 0.88 mmol) dropwise. The reaction mixture was

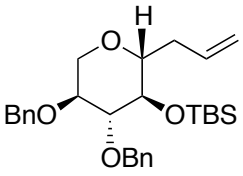
stirred for 2 h at 0 °C before the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (2:1 hexanes:ethyl acetate) provided 0.13 g diol **1.124** (87%, 2 steps) as a white solid. R_f 0.15 (2:1 hexanes:ethyl acetate); m.p. 120-122 °C; $[\alpha]^{20}_D$ = +24.9° (c = 0.45, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.25 (m, 10H), 5.01 (d, *J* = 11.5 Hz, 1H), 4.79 (d, *J* = 11.5 Hz, 1H), 4.69 (d, *J* = 11.0 Hz, 1H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.02 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.81 (dd, *J* = 12.2, 2.9 Hz, 1H), 3.70 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.60 (ddd, *J* = 9.5, 9.5, 5.4 Hz, 1H), 3.52 (dd, *J* = 8.7, 8.7 Hz, 1H), 3.46 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.27-3.20 (m, 2H), 3.04 (s, 1H), 2.62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 138.3, 128.8, 128.8, 128.2, 128.1, 128.1, 85.7, 80.0, 78.5, 75.4, 73.3, 70.5, 68.2, 62.7; IR (neat) 3468, 3333, 3031, 2926, 2860, 1603, 1455, 1363, 1119, 1096, 1057 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{20}H_{24}O_5Na$ 367.2 ($M+Na^+$), found 367.1.



1.125

Preparation of triflate 1.125. To a solution of diol **1.124** (0.15 g, 0.45 mmol) and 2,6-lutidine (0.16 mL, 1.4 mmol) in CH_2Cl_2 (10 mL) at -78 °C was added trifluoromethanesulfonic anhydride (0.079 mL, 0.47 mmol). After 30 min TBSOTf (0.11 mL, 0.50 mmol) was added, and the reaction mixture was slowly warmed to rt before the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) provided **1.125** (0.22

g, 85%) as a colorless oil. R_f 0.50 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +48.7° (c = 0.60, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.31 (d, *J* = 6.9 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 2H), 7.13-7.04 (m, 6H), 5.07 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.59 (dd, *J* = 10.7, 1.4 Hz, 1H), 4.33 (dd, *J* = 10.8, 4.9 Hz, 1H), 4.17 (d, *J* = 11.7 Hz, 1H), 4.13 (d, *J* = 11.8 Hz, 1H), 3.76 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.43 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.35 (ddd, *J* = 10.3, 8.8, 5.4 Hz, 1H), 3.19 (dd, *J* = 8.8, 8.8 Hz, 1H), 2.96 (ddd, *J* = 9.8, 5.4, 2.0 Hz, 1H), 2.88 (dd, *J* = 10.7, 10.7 Hz, 1H), 0.89 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.3, 138.3, 128.4, 128.3, 127.8, 127.8, 127.3, 127.0, 119.0, 85.1, 78.9, 78.2, 75.3, 74.6, 72.6, 70.2, 67.6, 25.8, 18.0, -3.8, -5.2; IR (neat) 3033, 2931, 2859, 1601, 1458, 1416, 1248, 1209, 1145, 1097 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{27}H_{38}F_3O_7SSi$ 591.2 ($M+H^+$), found 591.0.



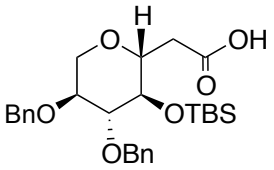
1.127

Preparation of alkene 1.127. To a solution of trimethylsilylacetylene (0.23 mL, 1.6 mmol) in THF (10 mL) at 0 °C was added *n*BuLi (0.65 mL of 2.5 M solution in hexanes, 1.62 mmol). After 30 min the reaction mixture was cooled to -78 °C. To this was transferred a solution of **1.125** (0.19 g, 0.32 mmol) and HMPA (0.28 mL, 1.6 mmol) in THF (4 mL). The reaction mixture was slowly warmed to rt over 2 h before the reaction was quenched with sat. NH_4Cl (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the organic extracts were dried (Na_2SO_4) and concentrated.

To a solution of the resulting residue in methanol (20 mL) was added potassium carbonate (45 mg, 0.32 mmol). The reaction mixture was stirred for 12 h at rt and

concentrated. Flash chromatography (10:1 hexanes-ethyl acetate) provided 0.13 g **1.126** (85%) as a colorless oil.

To a solution of **1.126** (0.13 g, 0.29 mmol) in ethyl acetate (10 mL) was added quinoline (17 μL, 0.14 mmol) and Lindlar's Pd catalyst (15 mg). The reaction mixture was stirred under a balloon of H_2 (1 atm.) for 2 h before it was passed through a celite column using ethyl acetate and concentrated. Flash chromatography (10:1 hexanes-ethyl acetate)gave 0.13 g of **1.127** (100%) as a colorless oil. R_f 0.60 (5:1 hexanes-ethyl acetate); $[\alpha]^{20}_D$ = +38.0° (c = 0.55, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.23 (m, 10H), 5.88 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.12 (dd, *J* = 17.1, 1.4 Hz, 1H), 5.10 (partially obscured d, *J* = 10.2 Hz, 1H), 5.08 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.00 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.62 (ddd, *J* = 10.3, 8.8, 4.9 Hz, 1H), 3.43 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.36 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.22-3.16 (m, 2H), 2.67-2.60 (m, 1H), 2.12-2.08 (m, 1H), 0.92 (s, 9H), 0.09 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4, 138.4, 135.4, 128.7, 128.4, 128.1, 128.0, 127.5, 127.4, 117.0, 86.0, 81.1, 79.7, 75.0, 74.7, 73.3, 68.2, 36.8, 26.3, 18.4, -3.3, -4.1; IR (neat) 3067, 2956, 2929, 2856, 1497, 1363, 1253, 1093 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{28}H_{40}O_4SiNa$ 491.3 ($M+Na^+$), found 491.2.

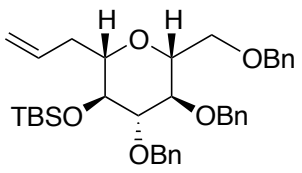


1.120

Preparation of acid 1.120. O_3 was bubbled through a solution of **1.127** (0.14 g, 0.30 mmol) in CH_2Cl_2 (20 mL) at -78 °C until the reaction mixture was a light blue color. Excess O_3 was purged from the reaction mixture by bubbling N_2 until the light

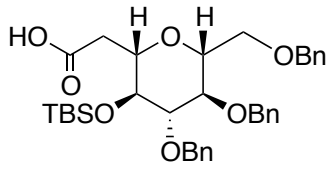
blue color dissipated. Triphenylphosphine (0.24 g, 0.90 mmol) was then added and the mixture was allowed to slowly warm to rt. After 12 h, the solution was concentrated under reduced pressure. Flash chromatography (50:1 to 5:1 hexanes:ethyl acetate) provided 0.12 g aldehyde **1.128** (81%) as a colorless oil.

A mixture of **1.128** (0.12 g, 0.25 mmol), THF (3 mL), *t*BuOH (3 mL), H_2O (3 mL), 2-Me-2-butene (0.60 mL, 5.7 mmol), NaH_2PO_4 (0.15 g, 1.2 mmol) and $NaClO_2$ (0.11 g, 1.25 mmol) was stirred at rt for 2 h. To this was added H_2O (8 mL) and the resulting mixture was extracted with ethyl acetate (3 x 10 mL). The extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate to pure ethyl acetate) provided acid **1.120** (0.11 g, 91%) as a colorless oil. R_f = 0.10 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +26.7° (c = 0.33, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44-7.28 (m, 10H), 5.12 (d, *J* = 11.2 Hz, 1H), 4.82 (d, *J* = 11.2 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.03 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.70-3.64 (m, 2H), 3.50 (dd, *J* = 8.3, 8.3 Hz, 1H), 3.45 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.28 (dd, *J* = 11.0, 11.0 Hz, 1H), 2.94 (dd, *J* = 15.1, 1.9 Hz, 1H), 2.41 (dd, *J* = 15.1, 9.8 Hz, 1H), 0.96 (s, 9H), 0.12 (s, 3H), 0.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 139.2, 138.3, 128.7, 128.6, 128.4, 128.2, 128.2, 127.5, 85.8, 79.5, 78.2, 75.2, 74.2, 73.4, 68.3, 38.2, 26.3, 18.3, -3.4, -4.2; IR (neat) 3500-2660 (broad), 3064, 2930, 2858, 1714, 1497, 1458, 1324, 1255, 1131, 1093 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{27}H_{39}O_6$ 487.2 ($M+H^+$), found 487.2.



1.130

Preparation of alkene 1.130. To a solution of **1.129** (0.22 g, 0.47 mmol) and 2,6-lutidine (0.17 mL, 1.4 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added TBSOTf (0.13 mL, 0.57 mmol) dropwise. The reaction mixture was stirred overnight before the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) provided 0.25 g **1.130** (90%) as a colorless oil. R_f 0.40 (10:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -18.4° (c = 0.76, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.25 (m, 13H), 7.10-7.08 (m, 2H), 6.02 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.18 (dd, *J* = 17.1, 1.0 Hz, 1H), 5.14 (dd, *J* = 10.2, 1.0 Hz, 1H), 5.05 (d, *J* = 12.2 Hz, 1H), 4.88 (d, *J* = 11.7 Hz, 1H), 4.75 (d, *J* = 10.7 Hz, 1H), 4.70 (d, *J* = 12.2 Hz, 1H), 4.63 (d, *J* = 12.2 Hz, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 3.79 (dd, *J* = 11.2, 2.0 Hz, 1H), 3.76 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.71 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.52 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.50-3.46 (m, 2H), 3.26 (ddd, *J* = 9.2, 9.2, 2.1 Hz, 1H), 2.65 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.24 (ddd, *J* = 15.2, 9.3, 6.4 Hz, 1H), 0.96 (s, 9H), 0.15 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 138.6, 138.3, 135.7, 128.6, 128.6, 128.4, 128.2, 128.1, 127.9, 127.8, 127.3, 126.9, 116.8, 87.2, 80.9, 79.4, 79.3, 75.2, 75.1, 75.0, 73.7, 69.1, 36.5, 26.3, 18.4, -3.3, -3.9; IR (neat) 3066, 3031, 2929, 2857, 1456, 1360, 1254, 1104, 1063 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{36}H_{49}O_5Si$ 589.3 ($M+H^+$), found 589.1.

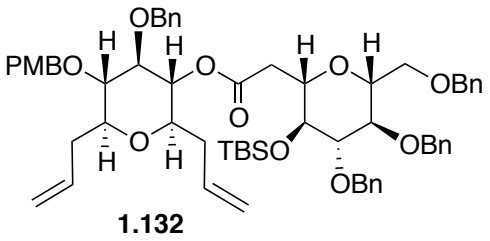


1.121

Preparation of acid 1.121. O_3 was bubbled through a solution of **1.120** (0.24 g, 0.41 mmol) in CH_2Cl_2 (20 mL) at -78 °C until the reaction mixture maintained a light

blue color. Excess O_3 was purged from the reaction mixture by bubbling N_2 through it for 20 min until the light blue color dissipated. Triphenylphosphine (0.32 g, 1.23 mmol) was then added and the mixture was allowed to slowly warm to rt. After 12 h, the solution was concentrated. Flash chromatography (50:1 to 5:1 hexanes:ethyl acetate) provided 0.22 g aldehyde **1.131** (91%) as a colorless oil.

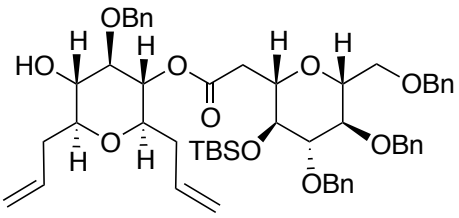
A mixture of **1.131** (0.22 g, 0.37 mmol), THF (3 mL), *t*BuOH (3 mL), H_2O (3 mL), 2-Me-2-butene (0.60 mL, 5.7 mmol), NaH_2PO_4 (0.22 g, 1.9 mmol) and $NaClO_2$ (0.17 g, 1.9 mmol) was stirred at rt for 2 h before the mixture was diluted with additional H_2O (10 mL). The resulting mixture was extracted with ethyl acetate (3 x 15 mL) and the extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate to 100% ethyl acetate) provided 0.22 g of acid **1.121** (96%) as a white solid. R_f 0.10 (1:1 hexanes:ethyl acetate); m.p. 119-120 °C; $[\alpha]^{20}_D$ = -6.3^o (c = 0.83, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.24 (m, 13H), 7.07-7.04 (m, 2H), 5.03 (d, *J* = 11.7 Hz, 1H), 4.86 (d, *J* = 11.7 Hz, 1H), 4.73 (d, *J* = 10.7 Hz, 1H), 4.66 (d, *J* = 12.2 Hz, 1H), 4.55 (d, *J* = 11.3 Hz, 2H), 3.77-3.70 (m, 4H), 3.56-3.46 (m, 3H), 2.90 (d, *J* = 15.6 Hz, 1H), 2.51 (dd, *J* = 15.6, 10.3 Hz, 1H), 0.92 (s, 9H), 0.12 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 139.1, 138.2, 138.1, 128.7, 128.6, 128.5, 128.2, 128.2, 128.0, 128.0, 127.4, 126.9, 86.9, 79.3, 79.0, 77.5, 75.3, 75.1, 74.2, 73.6, 68.7, 37.8, 26.2, 18.3, -3.4, -3.9; IR (neat) 3450-2700 (broad), 3032, 2930, 2893, 2858, 1714, 1497, 1406, 1255, 1098 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{35}H_{47}O_7Si$ 607.3 ($M+H^+$), found 607.1.



1.132

Preparation of ester 1.132. To a solution of acid **1.121** (0.69 g, 1.1 mmol) in THF (20 mL) was added triethylamine (0.57 mL, 4.1 mmol) and 2,4,6-trichlorobenzoyl chloride (0.44 mL, 2.8 mmol). The reaction mixture was heated at 40 °C for 2 h and then concentrated. To the resulting residue was transferred a solution of alcohol **1.101** (0.48 g, 1.1 mmol) in toluene (10 mL) followed by DMAP (0.53 g, 4.3 mmol). The reaction mixture was then heated at 40 °C for 12 h and then the reaction was quenched with sat. $NaHCO_3$ (aq., 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) provided 1.0 g **1.132** (87%) as a colorless oil. R_f 0.70 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -4.2° (c = 1.1, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.51-7.30 (m, 20H), 7.20-7.17 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.10-5.93 (m, 2H), 5.27-5.07 (m, 6H), 4.96 (d, *J* = 12.2 Hz, 1H), 4.90-4.82 (m, 4H), 4.69 (d, *J* = 10.3 Hz, 1H), 4.68 (d, *J* = 10.8 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.50 (d, *J* = 11.7 Hz, 1H), 3.94-3.77 (partially obscured m, 4H), 3.87 (s, 3 H), 3.68-3.42 (m, 7H), 3.03 (d, *J* = 13.7 Hz, 1H), 2.71 (dd, *J* = 14.2, 5.9 Hz, 1H), 2.58 (dd, *J* = 15.1, 10.2 Hz, 1H), 2.47-2.27 (m, 3H), 1.00 (s, 9H), 0.20 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 170.4, 159.7, 139.4, 138.9, 138.6, 138.5, 135.1, 134.5, 132.9, 130.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.9, 127.3, 126.9, 117.2, 117.0, 114.0, 86.8, 84.8, 81.5, 79.4, 79.0, 78.9, 77.9, 77.4, 75.3, 75.2, 75.1, 75.0, 74.5, 74.3, 73.6, 68.9, 55.5, 38.7, 36.3, 36.0, 26.1, 18.3, -3.5,

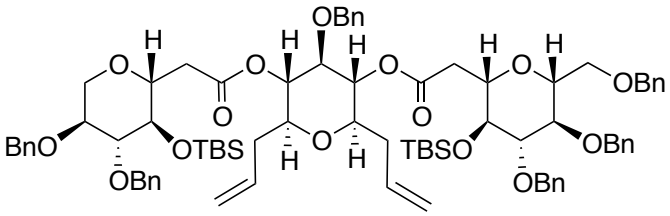
-4.2; IR (neat) 3066, 2931, 2858, 1749, 1514, 1456, 1361, 1250, 1094 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{61}H_{76}O_{11}SiNa$ 1035.5 ($M+Na^+$), found 1035.3.



1.133

Preparation of alcohol 1.133. To a mixture of **1.132** (0.25 g, 0.24 mmol) in CH_2Cl_2 (18 mL) and pH 7 phosphate buffer (2 mL) was added DDQ (0.073 g, 0.32 mmol). The reaction mixture was stirred for 2 h at rt before the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) provided 0.20 g **1.133** (90%) as a colorless oil. R_f 0.30 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -12.4° (c = 1.2, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.41-7.22 (m, 18H), 7.09-7.05 (m, 2H), 5.93 (partially obscured dddd, *J* = 17.1, 9.8, 6.9, 6.9 Hz, 1H), 5.84 (partially obscured dddd, *J* = 17.6, 10.8, 6.8, 6.8 Hz, 1H), 5.16-5.01 (m, 5H), 4.94 (dd, *J* = 9.3, 9.3 Hz, 1H), 4.84 (d, *J* = 12.2 Hz, 1H), 4.81 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 10.2 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 10.3 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 3.79 (ddd, *J* = 9.3, 2.0 Hz, 1H), 3.74 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.69 (dd, *J* = 10.7, 2.9 Hz, 1H), 3.57-3.37 (m, 7H), 3.26 (ddd, *J* = 8.3, 8.3, 3.5 Hz, 1H), 2.92 (dd, *J* = 15.1, 1.5 Hz, 1H), 2.60-2.54 (m, 1H), 2.47 (dd, *J* = 15.1, 10.3 Hz, 1H), 2.34-2.14 (m, 4H), 0.89 (s, 9H), 0.10 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 170.4, 139.3, 138.7, 138.5, 138.4, 134.9, 134.8, 134.4, 134.4, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.8, 127.2, 126.8, 117.1, 116.9, 86.7,

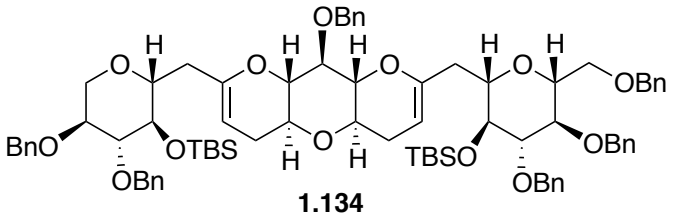
84.2, 79.2, 78.8, 78.7, 77.8, 77.3, 75.0, 75.0, 74.7, 74.1, 73.5, 68.8, 38.6, 36.2, 35.8, 25.9, 18.1, -3.7, -4.3; IR (neat) 3420 (broad), 2930, 2858, 1748, 1455, 1361, 1255, 1095 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{53}H_{68}O_{10}SiNa$ 915.5 ($M+Na^+$), found 915.3.



1.119

Preparation of diester 1.119. To a solution of acid **1.120** (0.12 g, 0.25 mmol) in THF (10 mL) was added triethylamine (0.13 mL, 0.93 mmol) and 2,4,6-trichlorobenzoyl chloride (0.10 mL, 0.64 mmol). The reaction mixture was heated at 40 °C for 2 h and then concentrated. To the resulting residue was transferred a solution of alcohol **1.133** (0.17 g, 0.19 mmol) in toluene (10 mL) followed by DMAP (0.12 g, 0.98 mmol). The mixture was heated at 40 ^oC for 12 h after which the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) provided 0.21 g **1.119** (99%) as a colorless oil. R_f 0.45 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +6.6° (c = 0.86, THF); ^1H NMR (500 MHz, CD_2Cl_2) δ 7.55-7.35 (m, 28H), 7.24-7.21 (m, 2H), 6.10-5.97 (m, 2H), 5.28-5.16 (m, 8H), 5.01 (d, *J* = 12.2 Hz, 1H), 4.94 (d, *J* = 11.2, 1H), 4.88 (d, *J* = 10.2 Hz, 1H), 4.80 (s, 2H), 4.74 (d, *J* = 10.7 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.6 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.00 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.96-3.53 (m, 14H), 3.30 (dd, *J* = 11.0, 11.0 Hz, 1H), 3.06 (dd, *J* = 15.1, 2.0 Hz, 1H), 3.02 (dd, *J* = 14.6, 2.0 Hz, 1H), 2.63 (dd, *J* = 14.6, 10.3 Hz, 1H), 2.57-2.46 (m, 3H), 2.43-2.34 (m, 2H), 1.08 (s, 9H),

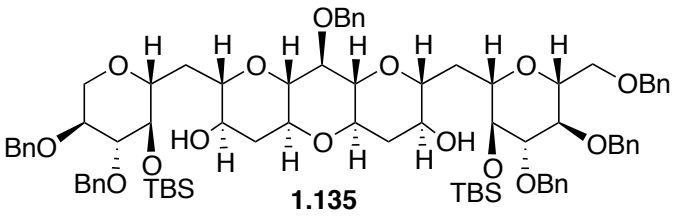
1.07 (s, 9H), 0.25 (s, 3H), 0.24 (s, 3H), 0.21 (s, 3H), 0.19 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 170.2, 170.1, 139.6, 139.4, 138.7, 138.6, 134.4, 134.3, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.5, 127.4, 127.0, 117.5, 117.3, 86.9, 85.7, 81.7, 79.6, 79.4, 79.0, 78.5, 77.9, 77.8, 77.7, 75.2, 75.1, 74.4, 74.3, 74.2, 73.8, 73.8, 73.7, 73.2, 68.9, 68.1, 38.7, 38.6, 35.9, 35.8, 26.1, 26.0, 18.3, 18.2, -3.6, -3.6, -4.2, -4.4; IR (neat) 2955, 2858, 1752, 1649, 1457, 1362, 1254, 1093 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{80}H_{104}O_{15}Si_2Na$ 1383.7 ($M+Na^+$), found 1383.4.



1.134

Preparation of tricycle 1.134. The general two-directional olefinic ester cyclization reaction protocol was carried out on diester **1.119** (0.21 g, 0.15 mmol) to give **1.134** (0.10 g, 50%) as a colorless oil. R_f 0.30 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +5.0^o (c = 0.60, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.50 (d, *J* = 7.7 Hz, 2H), 7.44-7.24 (m, 26H), 7.14-7.11 (m, 2H), 5.08 (d, *J* = 11.7 Hz, 1H), 5.02 (d, *J* = 11.7, 1H), 4.94 (s, 2H), 4.89 (d, *J* = 11.7 Hz, 1H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.74 (d, *J* = 11.7 Hz, 1H), 4.64 (broad d, *J* = 4.4 Hz, 1H), 4.61-4.54 (m, 6H), 3.97 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.74 (dd, *J* = 10.7, 1.5 Hz, 1H), 3.69-3.60 (m, 6H), 3.54 (dd, *J* = 8.3, 8.3 Hz, 1H), 3.52-3.38 (m, 7H), 3.33 (dd, *J* = 8.3, 8.3 Hz, 1H), 3.13 (dd, *J* = 10.8, 10.8 Hz, 1H), 2.70 (d, *J* = 14.5 Hz, 2H), 2.31-2.23 (m, 2H), 2.12-2.04 (m, 3H), 1.97 (dd, *J* = 14.7, 10.2 Hz, 1H), 0.93 (s, 9H), 0.92 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 151.1, 151.0, 139.6, 139.4, 139.3, 138.8, 138.7, 138.6, 128.5, 128.4, 128.3, 128.2, 128.0, 128.0, 127.8, 127.7, 127.7, 127.5, 127.4, 127.2, 127.1, 126.9, 94.8, 94.7,

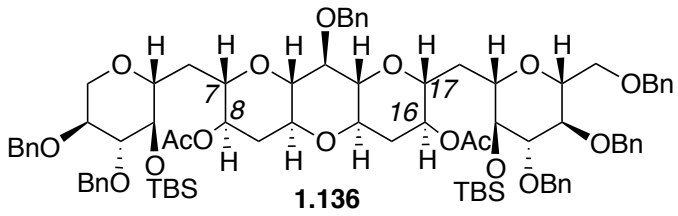
87.2, 85.9, 79.7, 79.5, 79.5, 79.1, 79.0, 78.4, 77.7, 75.1, 75.1, 75.0, 74.9, 74.9, 73.8, 73.3, 73.0, 72.4, 72.3, 69.4, 68.0, 36.9, 36.6, 27.7, 27.6, 26.1, 26.0, 18.2, 18.1, -3.6, -3.7, -4.1, -4.3; IR (neat) 3031, 2929, 2857, 1680, 1456, 1362, 1254, 1094 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{78}H_{100}O_{13}Si_2Na$ 1323.7 ($M+Na^+$), found 1323.1.



1.135

Preparation of diol 1.135. To a solution of **1.134** (18.7 mg, 0.0138 mmol) in CH_2Cl_2 (5 mL) at -78 °C was added of DMDO (0.55 mL of a 0.10 M solution in CH_2Cl_2, 0.055 mmol) dropwise. The reaction mixture was warmed to 0 °C and then concentrated. The a solution of the resulting residue in CH_2Cl_2 (5 mL) at -78 °C was added *i*Bu_2AlH (0.17 mL of a 1.0 M solution in hexanes, 0.17 mmol). After stirring for 2 h, the reaction was quenched with sat. NH_4Cl (aq., 5 mL) and allowed to warm to rt. Sat. potassium sodium tartrate solution (aq., 10 mL) was added and the mixture was stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (2:1 hexanes:ethyl acetate) provided 12.5 mg **1.135** (65%) as a colorless oil. R_f 0.50 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +4.9° (c = 0.37, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.44-7.24 (m, 28H), 7.12-7.06 (m, 2H), 5.08 (d, *J* = 11.7 Hz, 1H), 5.02 (d, *J* = 11.7, 1H), 4.90-4.85 (m, 3H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.59-4.48 (m, 5H), 3.98 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.69 (dd, *J* = 10.7, 2.0 Hz, 1H), 3.65-3.30 (m, 14H), 3.24-3.10 (m, 5H), 2.77 (d, *J* = 4.4 Hz, 1H), 2.34 (ddd, *J* = 11.2, 3.9, 3.9 Hz, 1H), 2.30-2.19 (m, 3H), 1.96 (ddd, *J* = 13.2, 9.3, 3.4 Hz, 1H), 1.83 (ddd, *J* = 13.2, 8.8, 3.9 Hz, 1H), 1.59 (s, 2H), 1.51-1.42 (m,

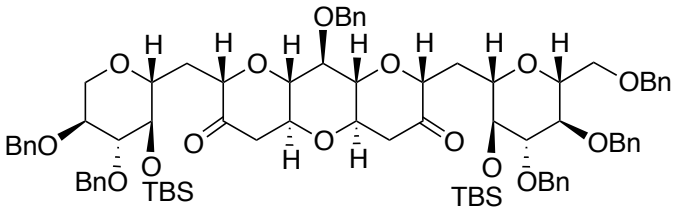
2H), 0.86 (s, 9H), 0.85 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 139.6, 139.4, 138.6, 138.4, 128.5, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.4, 127.2, 127.1, 126.8, 87.1, 85.9, 82.7, 82.7, 80.4, 79.6, 79.5, 78.9, 78.7, 78.4, 77.4, 75.2, 75.0, 74.8, 74.5, 73.6, 73.4, 73.0, 69.7, 68.9, 68.2, 67.8, 38.2, 34.3, 34.0, 26.1, 26.0, 18.2, -3.6, -3.7, -4.0, -4.1; IR (neat) 3420 (broad), 2929, 2858, 1456, 1363, 1253, 1090 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{78}H_{104}O_{15}Si_2Na$ 1359.7 ($M+Na^+$), found 1359.5.



1.136

Preparation of diacetate 1.136. To a solution of **1.135** (10 mg, 7.5 μmol) in CH_2Cl_2 (3 mL) at rt was added acetic anhydride (0.014 mL, 0.15 mmol) and triethylamine (0.042 mL, 0.30 mmol). After 2 h the reaction was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extract with CH_2Cl_2 (3 x 5 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) gave 10 mg **1.136** as a colorless oil (94%). R_f 0.30 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +12.1° (c = 0.32, THF); ^{1}H NMR (500 MHz, toluene) δ 7.65 (d, *J* = 7.3 Hz, 2H), 7.37-7.28 (m, 7H), 7.18-6.97 (m, 21 Hz), 5.16 (d, *J* = 12.2 Hz, 1H), 5.09 (d, *J* = 12.2, 1H), 5.06 (d, *J* = 11.7, 1H), 5.05 (ddd, *J* = 11.2, 11.2, 4.9 Hz, 1H), 5.00 (d, *J* = 12.2, 1H), 4.83 (ddd, *J* = 10.7, 10.7, 4.4 Hz, 1H), 4.75 (d, *J* = 12.2 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 11.2 Hz, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.51 (d, *J* = 12.2 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.16 (s, 2H), 3.84 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.79 (d, *J* = 9.3 Hz, 1H), 3.71-3.55 (m, 5H), 3.52-3.33 (m, 7H), 3.30 (dd, *J* = 8.3, 8.3 Hz,

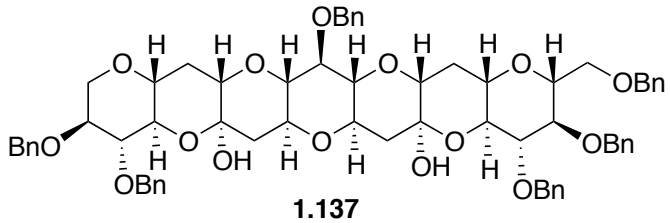
1H), 3.16 (ddd, *J* = 9.8, 9.8, 9.8 Hz, 2H), 3.02 (dd, *J* = 10.7, 10.7 Hz, 1H), 2.86 (ddd, *J* = 11.2, 9.3, 3.9 Hz, 1H), 2.77 (ddd, *J* = 11.7, 9.7, 3.9 Hz, 1H), 2.66 (ddd, *J* = 11.2, 4.4, 4.4 Hz, 1H), 2.57 (ddd, *J* = 10.7, 4.4, 4.4 Hz, 1H), 2.35-2.26 (m, 2H), 1.91 (ddd, *J* = 13.7, 8.8, 4.9 Hz, 1H), 1.83-1.75 (m, 1H), 1.72 (s, 6H), 1.41 (m, 2H), 0.93 (s, 9H), 0.92 (s, 9H), 0.09 (s, 6H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 169.7, 169.6, 139.6, 139.5, 138.7, 138.6, 128.4, 128.4, 128.3, 128.2, 128.2, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.4, 127.3, 127.1, 127.0, 126.8, 87.2, 86.0, 82.6, 82.2, 79.6, 79.2, 79.0, 78.9, 78.6, 77.5, 77.2, 76.9, 75.2, 74.9, 74.8, 74.7, 74.2, 74.1, 73.5, 73.2, 72.8, 71.4, 71.2, 69.5, 67.9, 35.5, 35.4, 34.8, 34.0, 26.1, 21.2, 18.2, 18.1, -3.7, -3.9, -4.1; IR (neat) 3032, 2927, 2856, 1742, 1457, 1364, 1237, 1093 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{82}H_{108}O_{17}Si_2Na$ 1443.7 ($M+Na^+$), found 1443.6.



1.118

Preparation of diketone 1.118. To a solution of **1.135** (53 mg, 0.040 mmol) in CH_2Cl_2 (5 mL) was added 4Å MS (10 mg), NMO (34 mg, 0.24 mmol) and TPAP (3 mg, 0.008 mmol). After stirring for 3 h, the reaction mixture was concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) gave **1.118** (48 mg, 92%) as a colorless oil. R_f 0.65 (2:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +7.8° (c = 0.23, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.64 (d, *J* = 7.8 Hz, 2H), 7.40-7.32 (m, 5H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.25-7.00 (m, 21H), 5.15 (d, *J* = 12.2 Hz, 1H), 5.12 (s, 2H), 5.03 (d, *J* = 11.7 Hz, 1H), 4.86 (d, *J* = 12.2 Hz, 1H), 4.80 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.46

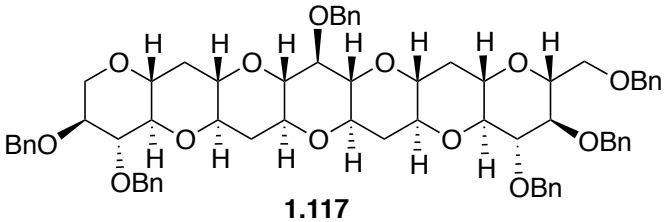
(d, *J* = 10.7 Hz, 1H), 4.35 (d, *J* = 12.2 Hz, 1H), 4.32 (d, *J* = 12.2 Hz, 1H), 4.30 (d, *J* = 11.7 Hz, 1H), 4.25 (d, *J* = 11.7 Hz, 1H), 4.00-3.95 (m, 2H), 3.87 (dd, *J* = 11.2, 5.4 Hz, 1H), 3.76 (ddd, *J* = 9.6, 9.6, 2.5 Hz, 1H), 3.65 (dd, *J* = 8.7, 8.7 Hz, 1H), 3.64-3.42 (m, 11H), 3.36-3.30 (m, 2H), 3.15 (ddd, *J* = 11.2, 9.7, 6.3 Hz, 1H), 3.07 (dd, *J* = 10.7, 10.7 Hz, 1H), 3.03 (partially obscured dd, *J* = 16.6, 5.8 Hz, 1H), 2.84 (dd, *J* = 16.0, 5.4 Hz, 1H), 2.73 (ddd, *J* = 13.7, 6.8, 2.4 Hz, 1H), 2.62 (ddd, *J* = 13.7, 7.3, 2.4 Hz, 1H), 2.34 (ddd, *J* = 12.2, 10.8, 2.0 Hz, 1H), 2.23-2.11 (m, 3H), 1.05 (s, 9H), 1.02 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 205.9, 205.6, 139.5, 139.4, 139.1, 138.6, 138.5, 138.4, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 12.4, 127.2, 127.1, 126.9, 87.1, 85.9, 80.8, 80.2, 79.9, 79.6, 79.5, 79.3, 79.3, 77.4, 76.1, 75.2, 75.1, 75.0, 74.1, 73.6, 73.5, 73.4, 73.0, 69.8, 68.0, 44.2, 44.0, 33.9, 33.6, 26.0, 18.2, 18.1, -3.7, -3.7, -4.0, -4.3; IR (neat) 3031, 2954, 2929, 2857, 1726, 1497, 1454, 1361, 1252, 1095 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{78}H_{100}O_{15}Si_2Na$ 1355.7 ($M+Na^+$), found 1355.3.



1.137

Preparation of dihemiacetal 1.137. To a solution of **1.118** (18.3 mg, 0.014 mmol) in THF (10 mL) was added HF•Py (2 mL, 0.11 mol). The reaction mixture was stirred at rt overnight before the reaction was quenched with sat. $NaHCO_3$ (20 mL). The aqueous phase was extract with ethyl acetate (3 x 10 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate) gave 13.8 mg **1.137** (91%) as a white solid. R_f 0.10 (2:1 hexanes:ethyl acetate);

m.p. 148-150 °C; $[\alpha]^{20}_D$ = -3.1° (c = 0.16, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.51 (d, *J* = 7.3 Hz, 2H), 7.45 (t, *J* = 6.8 Hz, 4H), 7.31-7.26 (m, 4H), 7.22-7.06 (m, 20H), 5.06 (d, *J* = 8.3 Hz, 1H), 5.04 (s, 2H), 5.01 (d, *J* = 12.7 Hz, 2H), 4.94 (d, *J* = 12.7 Hz, 1H), 4.90 (d, *J* = 12.2 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.46 (d, *J* = 12.2 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 2H), 4.04 (dd, *J* = 9.8, 9.8 Hz, 1H), 4.00-3.96 (m, 2H), 3.82 (dd, *J* = 8.3, 8.3 Hz, 1H), 3.80 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.73-3.49 (m, 8H), 3.36 (ddd, *J* = 9.3, 9.3, 4.9 Hz, 2H), 3.16 (dd, *J* = 10.7, 10.7 Hz, 1H), 3.09-3.04 (m, 2H), 2.96 (ddd, *J* = 8.5, 8.5, 8.5 Hz, 1H), 2.87 (ddd, *J* = 9.2, 9.2, 9.2 Hz, 1H), 2.57 (broad s, 1H), 2.48 (broad s, 1H), 2.28-2.16 (m, 6H), 1.82 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 2H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 139.5, 139.4, 139.3, 138.7, 138.7, 138.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 127.5, 93.6, 83.7, 83.5, 83.4, 82.8, 80.1, 79.7, 78.3, 78.1, 77.7, 75.3, 75.2, 74.9, 74.7, 74.6, 74.6, 74.4, 74.1, 73.9, 73.7, 73.5, 69.5, 69.0, 41.6, 30.0, 29.9; IR (neat) 3386 (broad), 3030, 2873, 1454, 1364, 1280, 1088 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{66}H_{72}O_{15}Na$ 1127.5 (M+Na$^+$), found 1127.2.



1.117

Preparation of heptacycle 1.117. To a solution of **1.137** (4.1 mg, 3.7 μmol) in CH_2Cl_2 (4 mL) and EtSH (1.0 mL, 14 mmol) at rt was added $Zn(OTf)_2$ (27 mg, 0.074 mmol). The reaction mixture was heated at reflux overnight and then cooled to rt. The reaction was quenched with triethylamine (1 mL). Filtration through a silica plug (2:1 hexanes:ethyl acetate) and concentration gave a colorless oil which was taken directly to the next step without further purification.

To a mixture of the residue from above and Ph_3SnH (26 mg, 0.074 mmol) in toluene (5 mL) at 110 °C was added AIBN (2 mL of a 0.002 M solution in toluene, 4 μmol) via syringe pump over 12 h. The reaction mixture was then cooled to rt and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) afforded 2.4 mg **1.117** as a white solid (61%, 2 steps). R_f 0.55 (2:1 hexanes:ethyl acetate); mp 250-253 °C; $[\alpha]^{20}_D$ = +11.6° (c = 0.16, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.54 (d, *J* = 7.9 Hz, 2H), 7.47 (d, *J* = 7.8 Hz, 2H), 7.44 (d, *J* = 7.3 Hz, 2H), 7.32-7.06 (m, 24H), 5.08 (d, *J* = 11.7 Hz, 1H), 5.04 (d, *J* = 12.2 Hz, 1H), 5.04 (d, *J* = 11.3 Hz, 1H), 4.98 (s, 2H), 4.88 (d, *J* = 11.7 Hz, 1H), 4.83 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.47 (d, *J* = 12.6 Hz, 1H), 4.44 (d, *J* = 12.2 Hz, 1H), 4.38 (d, *J* = 12.2 Hz, 1H), 3.94 (dd, *J* = 11.2, 5.9 Hz, 1H), 3.84 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.75-3.69 (m, 2H), 3.64 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.61-3.43 (m, 4H), 3.28-3.22 (m, 3H), 3.17 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.14 (dd, *J* = 11.0, 11.0 Hz, 1H), 2.98-2.80 (m, 8H), 2.43-2.30 (m, 4H), 1.68-1.56 (m, 4H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 139.4, 139.4, 139.3, 138.8, 138.7, 138.5, 128.5, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.8, 127.8, 127.7, 127.6, 127.5, 84.0, 83.1, 82.7, 82.6, 82.5, 82.4, 80.1, 79.6, 78.1, 77.9, 76.9, 76.7, 76.6, 75.2, 75.1, 74.9, 74.8, 74.3, 73.6, 73.5, 69.6, 68.9, 35.3, 35.3; IR (neat) 2921, 2857, 1650, 1455, 1430, 1091 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{66}H_{72}O_{13}Ag$ 1179.5 ($M+Ag^+$), found 1179.1.

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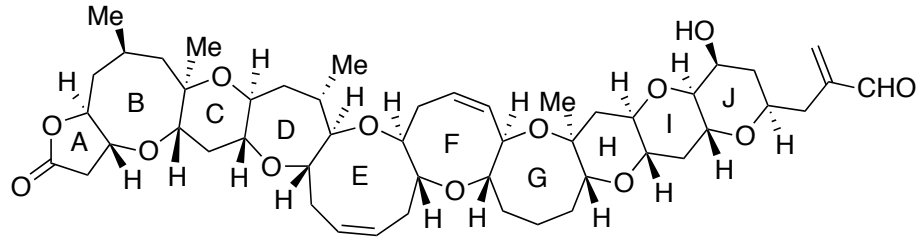
CHAPTER 2

TOTAL SYNTHESIS OF (-)-BREVENAL

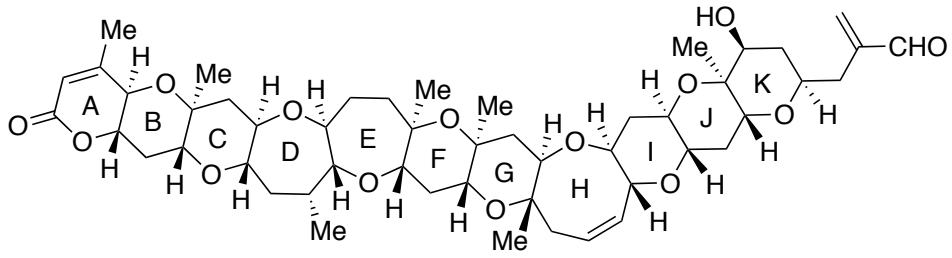
Introduction

The dinoflagellate-derived marine polycyclic ether natural products have attracted a lot of attention from the scientific community because of their unique structures and intriguing biological properties.[1] The marine dinoflagellate, *Karenia brevis*, which is common in Gulf of Mexico waters and responsible for toxic red tides in Florida and Texas, is host to a number of bioactive polycyclic ether compounds (Figure 2.1).[2] Among them, the members that have received the most attentions are the brevetoxins, which are a class of potent neurotoxins associated with the massive killings of fish and other marine animals, as well as human poisoning during red tide events.[3] Human consumption of shellfish contaminated with the brevetoxins results in neurotoxic shellfish poisoning (NSP), which involves a cluster of gastrointestinal and neurological symptoms such as ataxia, distal paresthesias, dizziness, nausea and vomiting.[4] In addition, inhalation of the airborne brevetoxins can cause respiratory irritations and bronchoconstriction in human and other marine mammals.[5]

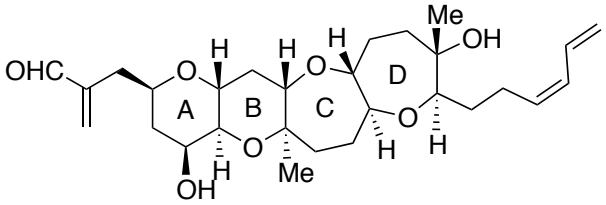
It has been shown that the brevetoxins exert their biological influence through binding to site 5 of voltage gated sodium channels (VGSC) in excitable membranes.[6] VGSC are a class of transmembrane proteins that conduct sodium ions based on electrical



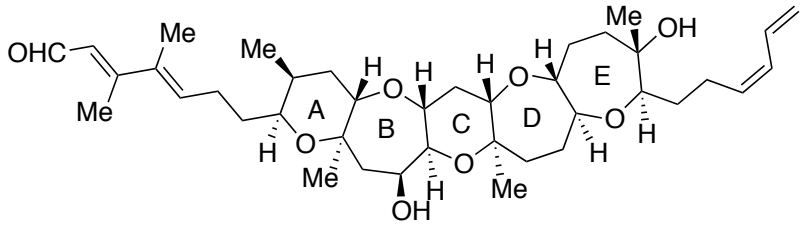
brevetoxin A (**2.1**)



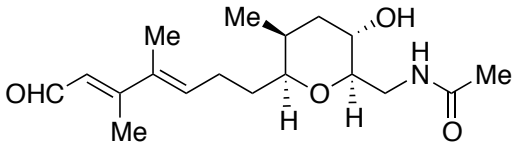
brevetoxin B (**2.2**)



hemibrevetoxin B (**2.3**)



brevenal (**2.4**)



brevisamide (**2.5**)

Figure 2.1. Representative polycyclic ether natural products isolated from *Karenia brevis*

potential difference across the membrane.[7] They play a central role in physiology by transmitting depolarizing impulses quickly throughout cell networks and enabling coordination of higher processes.[8] VGSC consist of a highly processed pore-forming α subunit that associates with auxiliary β subunits (Figure 2.2). The α subunit in VGSC has four homologous domains (I-IV), each containing six transmembrane α helices, labeled S1-S6. The binding of brevetoxins to VGSC takes place on S5 in a "head-down" fashion, which results in a prolonged mean channel open time, a shift of the channel activation potential to more negative values, and inhibition of channel inactivation (Figure 2.3). This in turn leads to persistent depolarization of the cell and ultimately causes cell death via calcium influx.[9]

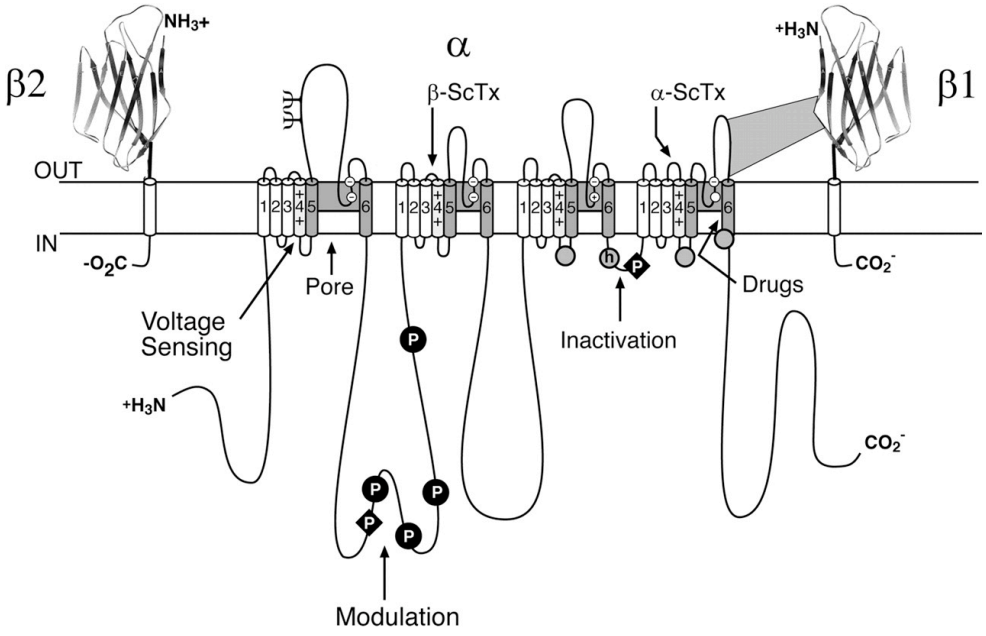


Figure 2.2. Schematic representation of the sodium channel subunits

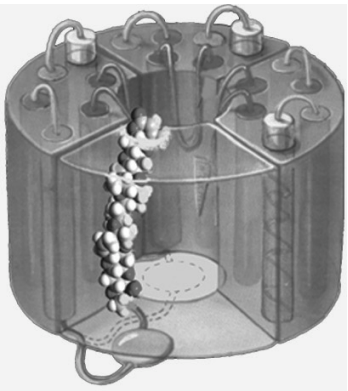


Figure 2.3. Brevetoxins binding to site 5 of VGSC

In 2004, Baden, Bourdelais, and co-workers isolated a new polycyclic ether natural product that they named brevenal (**2.4**) from laboratory cultures of *Karenia brevis*.[2c] Although brevenal is co-synthesized with the neurotoxic brevetoxins, it shows no toxicity even at micromolar concentrations in a fish bioassay. Exposure of the fish to both brevenal and brevetoxin B at equimolar concentrations results in fish living significantly longer than fish receiving brevetoxin B alone.[2c] In a rat brain synaptosome receptor binding assay, Baden, Bourdelais and co-workers showed that brevenal could inhibit binding of the brevetoxins to VGSC in a concentration-dependent manner.[2d] Gibson and co-workers also demonstrated that brevenal was able to both prevent and reverse the DNA damage caused by the brevetoxins in human lymphocytes.[10] These results suggest that brevenal is an antagonist of the brevetoxins and could be exploited as a template for the development of therapeutic treatments for red tide-related intoxications.

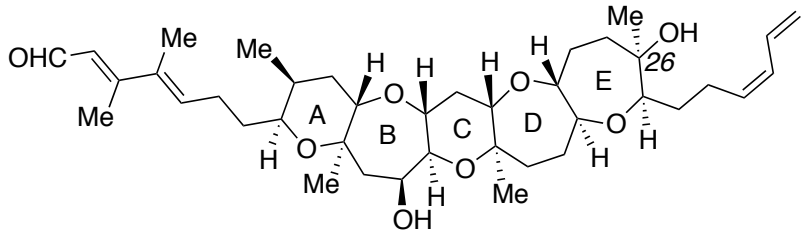
Equally interesting is that in a study conducted by Abraham and co-workers, brevenal was shown to be able to inhibit bronchoconstriction that was induced by inhalation of aerosolized brevetoxins in a sheep model.[11] The researchers also discovered

that brevenal was able to increase tracheal mucus velocity at picomolar concentrations, which represents a million-fold lower dose than amiloride, a sodium channel blocker that is currently used in the treatment of cystic fibrosis.[11] These intriguing results suggest that brevenal may also serve as a potential lead compound for therapeutic treatments of mucociliary dysfunction associated with lung disorders.

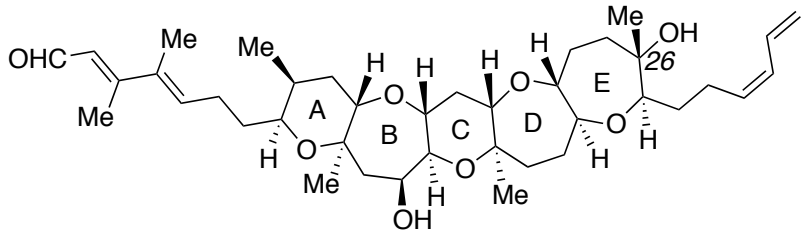
In addition to its fascinating biological profile, brevenal is also an attractive target from a synthetic point of view. It has a *trans*-fused 6,7,6,7,7-pentacyclic polyether backbone, which is absent in any other marine polycyclic ether natural products. Although brevenal is approximately half the size of brevetoxins, it is densely functionalized with four methyl groups, three of them being angular, and two hydroxy groups on the pentacyclic core, together with a unique 3,4-dimethyl substituted conjugated (*E,E*)-dienal side chain.

Previous Synthetic Studies Towards Brevenal

Because of its unique structure and intriguing biological activity, brevenal has received attention from the synthetic community. In 2006, only two years after the isolation and structure elucidation were reported, Sasaki and co-workers completed the first total synthesis of the proposed structure of brevenal (**2.6**, Figure 2.4), which ultimately led to a structure revision of the stereochemistry on C26.[12] Later in the same year, Sasaki and co-workers verified the revised structure through total synthesis and established the absolute configuration of brevenal (**2.4**).[13] So far, there have been three total syntheses including ours, and one partial synthesis of brevenal. The following is a brief summary of previous synthetic studies towards brevenal from other research groups.



originally proposed structure of brevenal (**2.6**)



brevenal (**2.4**)

Figure 2.4. Originally proposed and revised structure of brevenal

Sasaki's Total Synthesis of Brevenal

Sasaki's retrosynthetic analysis of the revised structure of brevenal is shown in Figure 2.5. The two side chains were to be installed at the very late stage using a Wittig reaction and a Stille coupling respectively.[13] The pentacyclic core **2.7** was envisioned to be constructed from a Suzuki-Miyaura coupling between the AB ring enol phosphate **2.8** and the DE ring exocyclic alkene **2.9**.

Sasaki's synthesis of the AB ring fragment **2.8** started with a highly diastereoselective Evans aldol condensation between aldehyde **2.10** and chiral oxazolidinone **2.11** to generate two stereocenters, which represented C8 and C9 in brevenal (Figure 2.6). The chiral auxiliary was subsequently removed, and allylic alcohol **2.13** was obtained after seven steps. Sharpless epoxidation of the allylic alcohol, Parikh-Doering oxidation, and a Wittig olefination afforded chiral epoxide **2.14**. Once the PMB

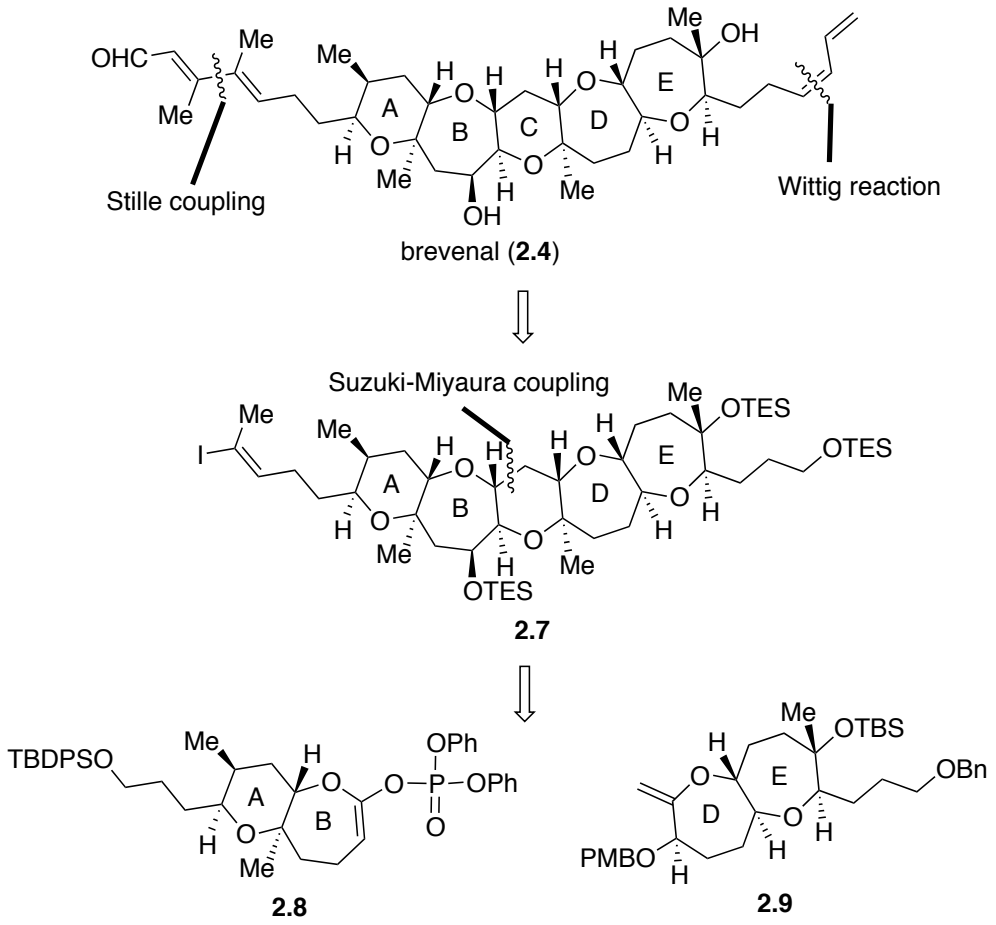


Figure 2.5. Sasaki's retrosynthetic analysis of brevenal

group was removed, the resulting free hydroxy group attacked the epoxide in a 6-*endo* fashion to furnish the A ring pyran **2.15** after protecting the resulting secondary alcohol as a TES ether. Seco-acid **2.16** was subsequently generated in five steps, which was subjected to the Yamaguchi lactonization to give the B ring lactone **2.17**. Finally, the requisite AB ring C16 enol phosphate **2.8** was obtained after treating the lactone with KHMDS and $(PhO)_2P(O)Cl$.

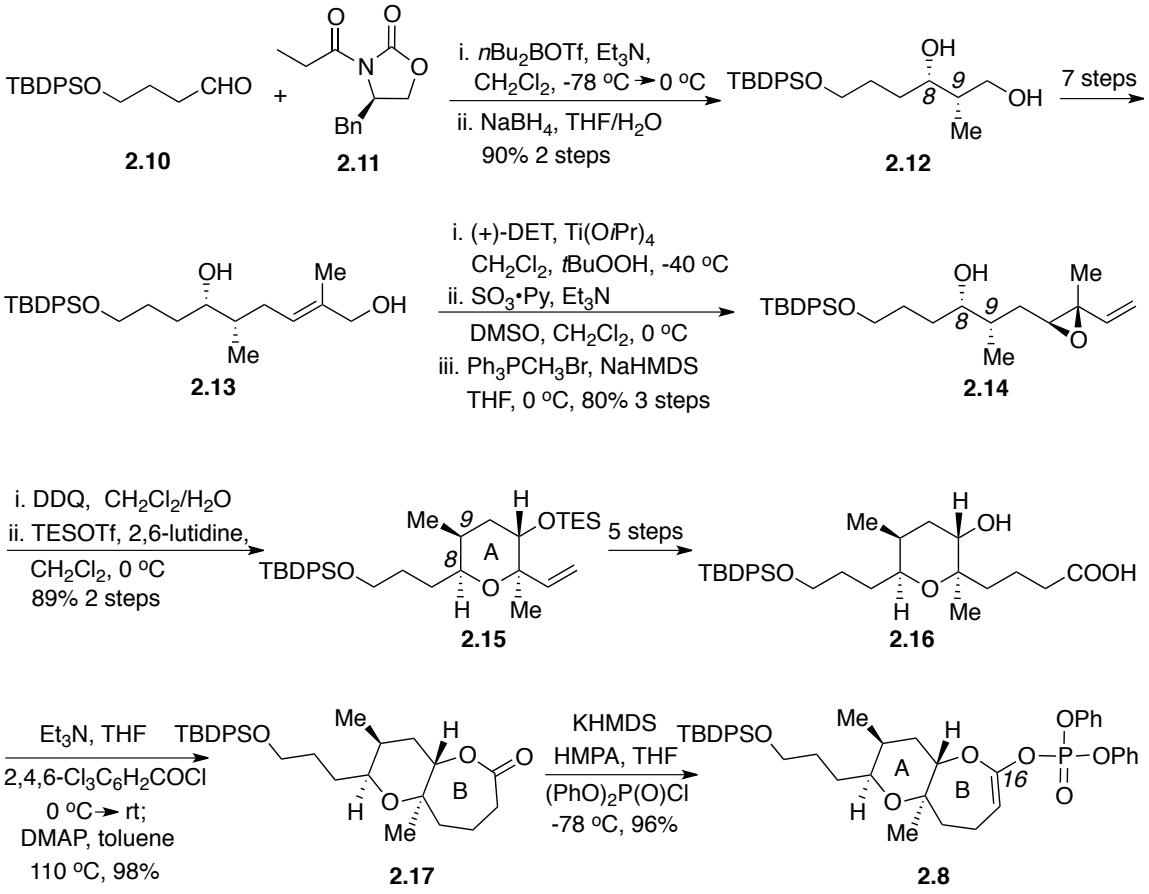


Figure 2.6. Sasaki' synthesis of the AB ring coupling partner **2.8**

Sasaki's approach to the DE fragment started from 2-deoxy-D-ribose (**2.18**, Figure 2.7). In 11 steps, they obtained stannyl aldehyde **2.19**, which underwent an intramolecular cyclization upon treatment with BF_3•OEt_2 to give the D ring of brevenal **2.20** as a single stereoisomer.[14] Ketoester **2.21** was then formed after nine steps, which when subjected to SmI_2, a radical reductive cyclization proceeded smoothly to give the tricyclic lactone **2.22** along with its corresponding hydroxy ester **2.23** with excellent stereoselectivity and good overall yield. Both **2.22** and **2.23** were subsequently reduced to diol **2.24**, which was transformed to the DE ring coupling partner **2.9** in 11 steps.

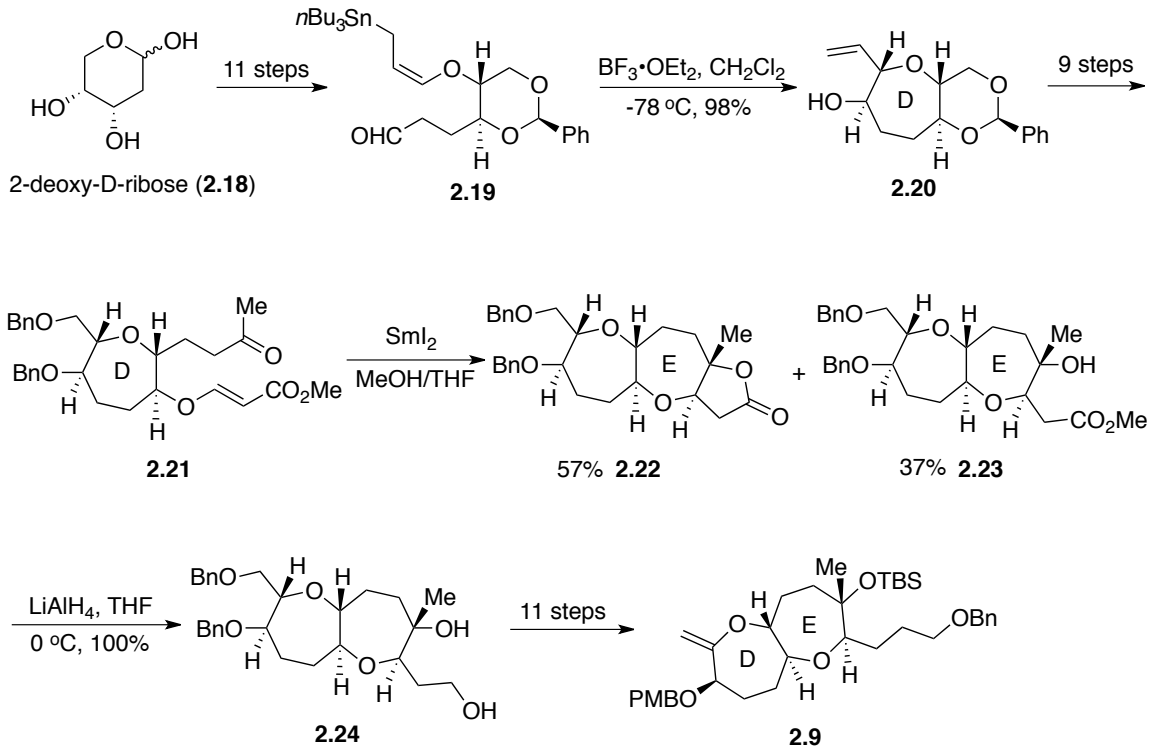


Figure 2.7. Sasaki's synthesis of the DE ring coupling partner **2.9**

Sasaki's coupling of the AB ring enol phosphate and the DE ring alkene was achieved using a Suzuki-Miyaura reaction (Figure 2.8). The obtained enol ether **2.25** underwent a stereoselective hydroboration to give a secondary alcohol, which was subsequently oxidized to afford ketone **2.26** as a single stereoisomer. The C14 hydroxy group was installed stereoselectively using a Rubottom oxidation to give ketone **2.27**, which was converted into C19 ketone **2.28** in another four steps. Treatment of **2.28** with $Zn(OTf)_2$ and EtSH removed both TES groups and simultaneously promoted C ring cyclization to give *O*,*S*-mixed ketal **2.29**. After reprotecting the remaining hydroxy group, angular methyl installation using *m*CPBA and $AlMe_3$ successfully gave the brevenal pentacyclic core **2.30**. It took Sasaki and co-workers another 18 steps to install the two side chains of brevenal, and the spectral data of the final product matched that in

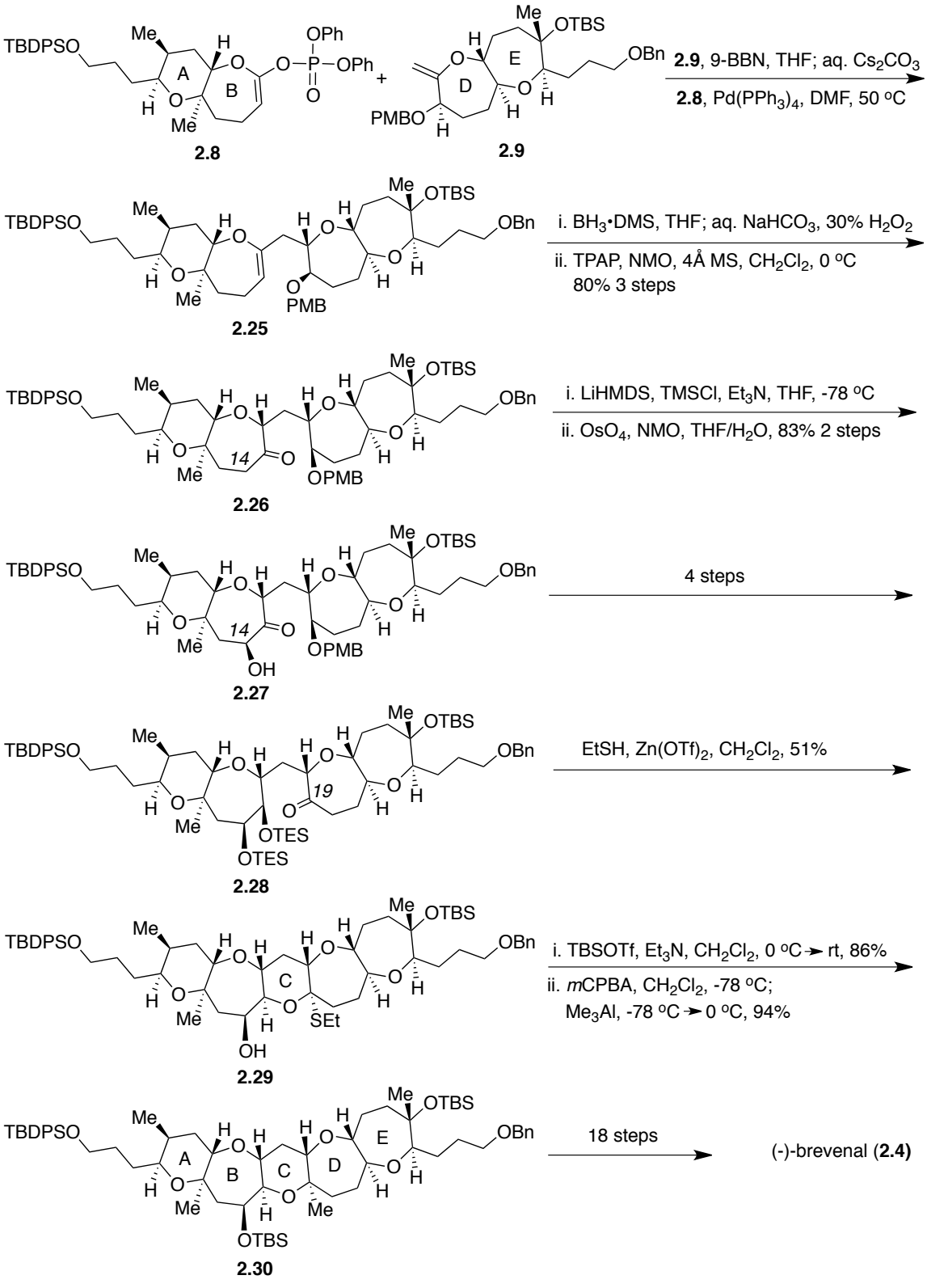


Figure 2.8. Sasaki's synthesis of brevenal pentacyclic core

the isolation paper. Thus, Sasaki and co-workers achieved the first total synthesis of (-)-brevenal in 64 steps (longest linear sequence, 46 steps to the pentacyclic core), and also corrected the originally proposed structure.

The highlight of Sasaki's synthesis was the highly convergent Suzuki-Miyaura coupling of two complex intermediates. However, Sasaki and co-workers considered that the routes to synthesize both the AB and the DE coupling partners were too long (23 steps and 34 steps respectively), which had compromised the efficiency of their synthesis. To solve this problem, they adopted a different retrosynthetic plan in their 2nd generation synthesis of brevenal's pentacyclic core (Figure 2.9).[15] In this new approach, they still exploited the powerful Suzuki-Miyaura reaction, but switched the roles of the two coupling partners, with AB ring fragment **2.32** as the exocyclic alkene and DE ring fragment **2.33** as the enol phosphate. In addition, the hydroxy group on C14 was preinstalled before the coupling. With the new synthetic plan, Sasaki and co-workers was able to synthesize brevenal pentacyclic core **2.31** in 32 steps, compared to 46 steps in the previous synthesis.

Kadota's Total Synthesis of Brevenal

In 2009, Kadota and co-workers reported their total synthesis of brevenal (Figure 2.10).[16] As in Sasaki's synthesis, Kadota also proposed a late stage installation of the two side chains, but with a shorter strategy using a Wittig reaction and a Horner-Wadsworth-Emmons reaction respectively. The pentacyclic core of brevenal in their synthesis was envisioned to come from stannyl α-acetoxy ether **2.35** using an intramolecular allylation

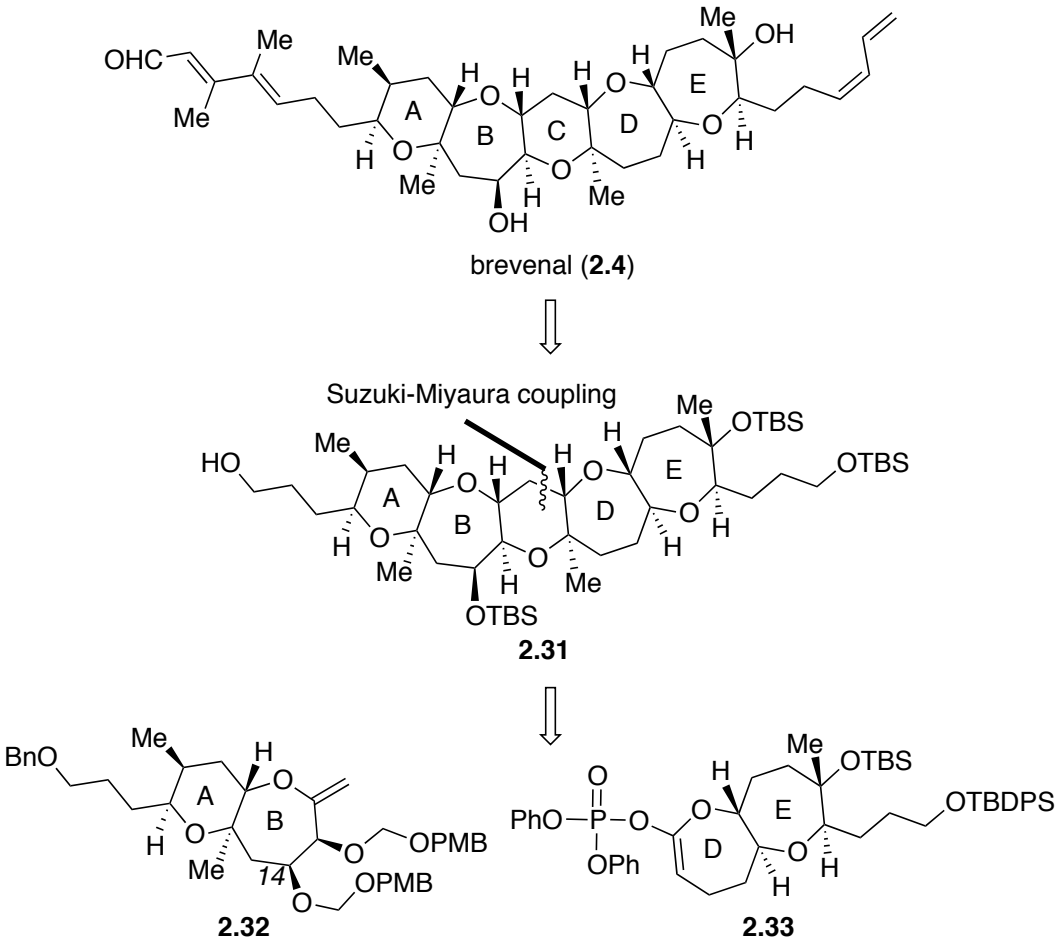


Figure 2.9. Sasaki's 2nd generation retrosynthetic analysis of brevenal

and ring-closing metathesis reaction sequence. The α-acetoxy ether **2.35** would in turn be obtained from the ABC ring acid **2.36** and alcohol **2.37**.

Kadota and co-workers commenced their synthesis of the ABC ring coupling partner **2.36** from 2-deoxy-D-ribose (**2.18**), which was converted into hydroxy epoxide **2.38** in 10 steps (Figure 2.11). Upon treatment with PPTS, **2.38** underwent a 6-*endo* cyclization to give the C ring of brevenal. In another 10 steps, Kadota and co-workers stereoselectively installed the C14 hydroxy group and synthesized seco-acid **2.40**, which

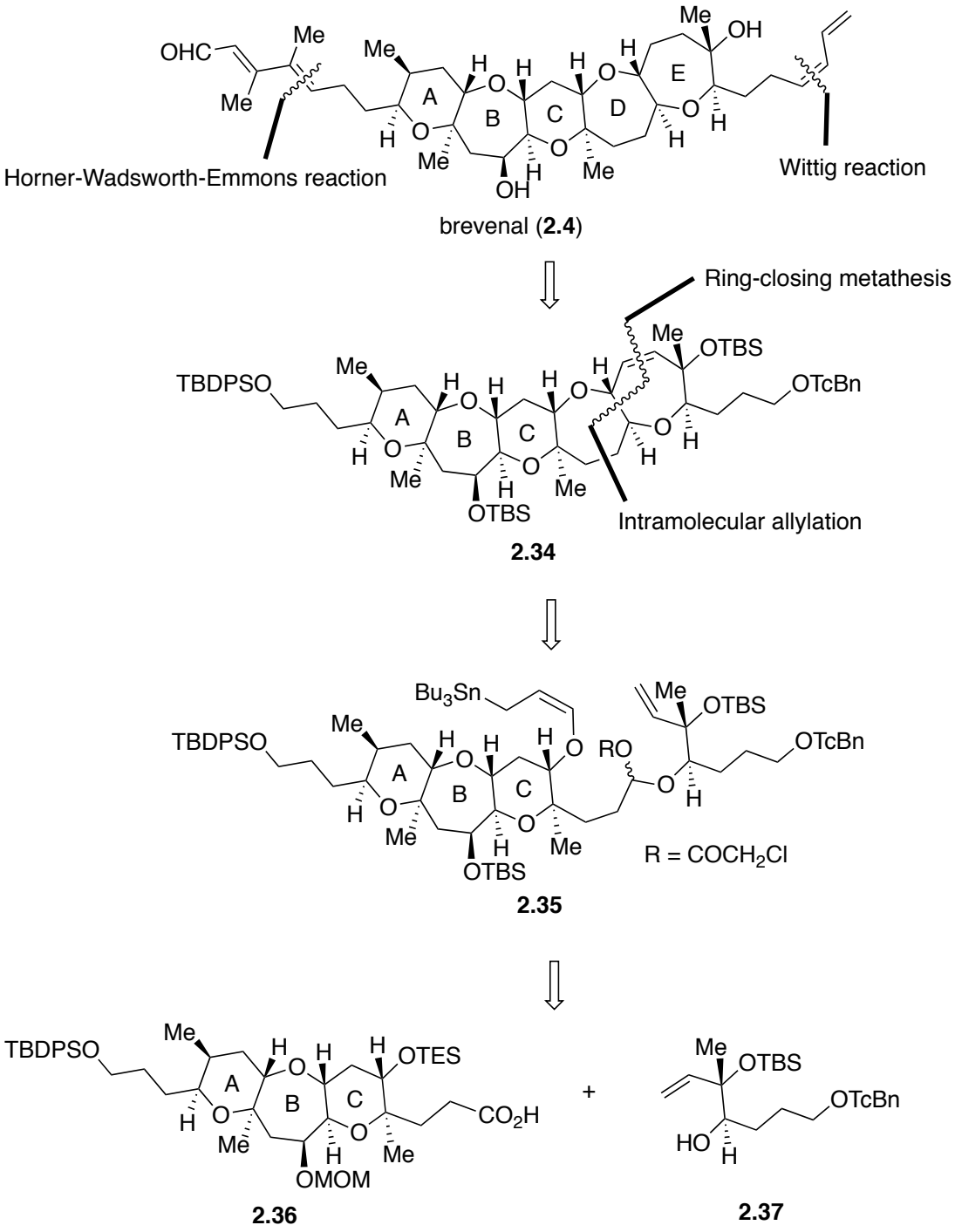


Figure 2.10. Kadota's retrosynthetic analysis of brevenal

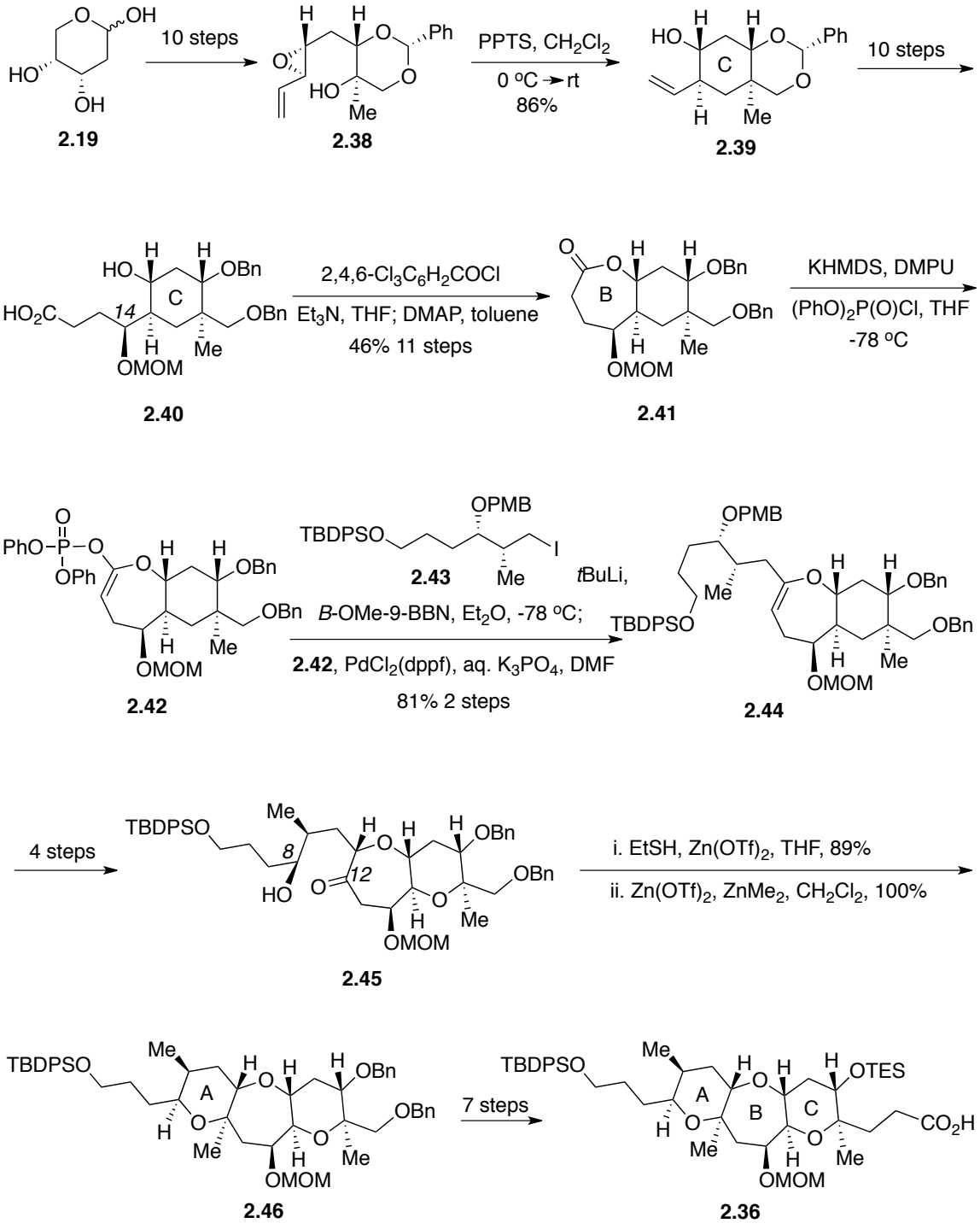


Figure 2.11. Kadota's synthesis of the A-C ring coupling partner **2.36**

was converted into B ring lactone **2.41** using Yamaguchi's conditions. The lactone was then converted to enol phosphate **2.42** and coupled with iodide **2.43** using a Suzuki-Miyaura reaction to give enol ether **2.44**. In four steps, **2.44** was transformed into hydroxy ketone **2.45**, which upon treatment with $Zn(OTf)_2$ and EtSH gave an *O,S*-mixed ketal. A novel methyl addition to the mixed ketal using $ZnMe_2$ and $Zn(OTf)_2$ successfully furnished the ABC ring skeleton of brevenal as **2.46**,[17] which was converted into the coupling partner **2.36** in another seven steps.

The coupling between acid **2.36** and known alcohol **2.37**[18] was accomplished using a Yamaguchi esterification to give ester **2.47** (Figure 2.12). In four steps, the C18 TES protected alcohol was converted to stannyl enol ether **2.48**. Half reduction of the ester with $i Bu_2AlH$ and a subsequent quench with chloroacetic anhydride afforded α-chloroacetoxy ether **2.35**, which upon treatment with $MgBr_2 \bullet OEt_2$ underwent an intramolecular allylation to give the D ring of brevenal **2.49** as a single stereoisomer. Subsequent ring-closing metathesis using Grubbs' 1st generation catalyst **2.50** successfully furnished the pentacyclic core of brevenal **2.34**. The side chains were installed in another twelve steps to complete the total synthesis of brevenal.

Kadota's total synthesis of brevenal required 45 steps to the pentacyclic core and 57 steps to the final product (both for the longest linear sequence). Although the synthetic strategy is not as convergent as Sasaki's, it features an efficient intramolecular allylation and ring-closing metathesis reaction sequence to generate the pentacyclic core of brevenal and a more concise introduction of the side chains.

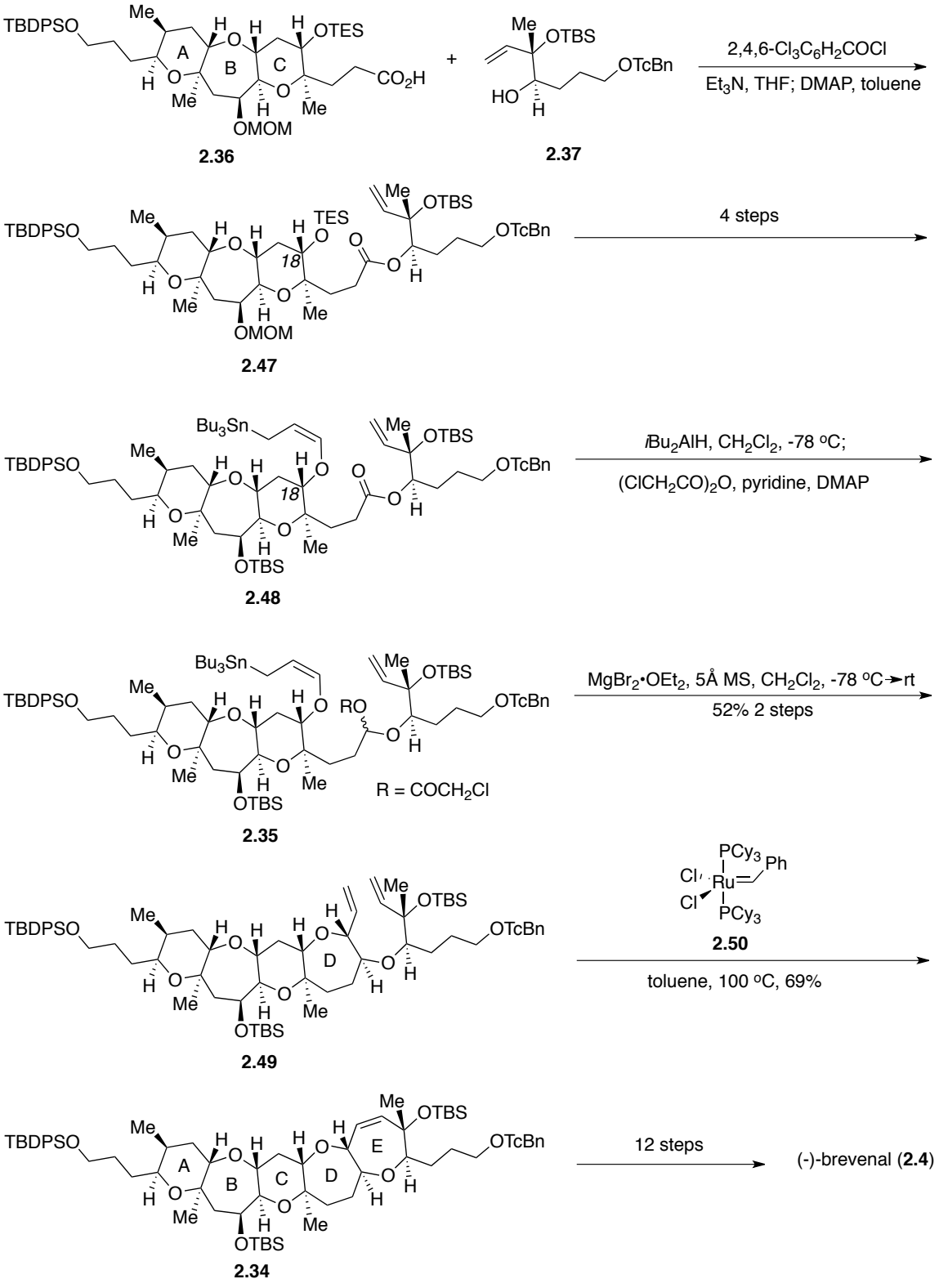


Figure 2.12. Kadota's synthesis of brevenal pentacyclic core

Crimmins' Partial Synthesis of Brevenal

In 2010, Crimmins and co-workers reported their efforts towards the synthesis of brevenal. Their retrosynthetic plan is shown in Figure 2.13.[19] The proposed strategy was centered on a convergent coupling of AB ring phosphonate **2.53** and E ring aldehyde **2.54** through a Horner-Wadsworth-Emmons reaction and an acid-catalyzed cyclization to generate the D ring.

Crimmins' synthesis of the AB ring fragment **2.53** commenced with a Horner-Wadsworth-Emmons reaction between aldehyde **2.55** and phosphonate **2.56** to give a α,β-unsaturated ketone, which after 1,4-reduction and removal of the TMS group afforded **2.57** (Figure 2.14). An acid-catalyzed cyclization subsequently furnished the A ring of brevenal as enol ether **2.58**, which was converted into the acyl oxazolidinone **2.59** in another ten steps. A highly diastereoselective glycolate alkylation at C16 afforded nitrile **2.60**.[20] After converting the chiral auxiliary into an alkene to give **2.61**, ring-closing metathesis using Grubbs' 2nd generation catalyst **2.62** successfully furnished the B ring of brevenal **2.63**, which was transformed into the AB ring coupling precursor **2.53** in five steps.

The E ring fragment synthesis started with a highly diastereoselective aldol reaction between oxazolidinone **2.64** and aldehyde **2.65** to generate the C26 quaternary center of brevenal (Figure 2.15). After eight steps, another oxazolidinone **2.67** was obtained, to which Crimmins and co-workers applied their glycolate alkylation strategy again to give nitrile **2.68**. The chiral auxiliary was then removed, and diene **2.69** was obtained from **2.68** in three steps. Upon treatment of **2.69** with Grubbs' 2nd generation

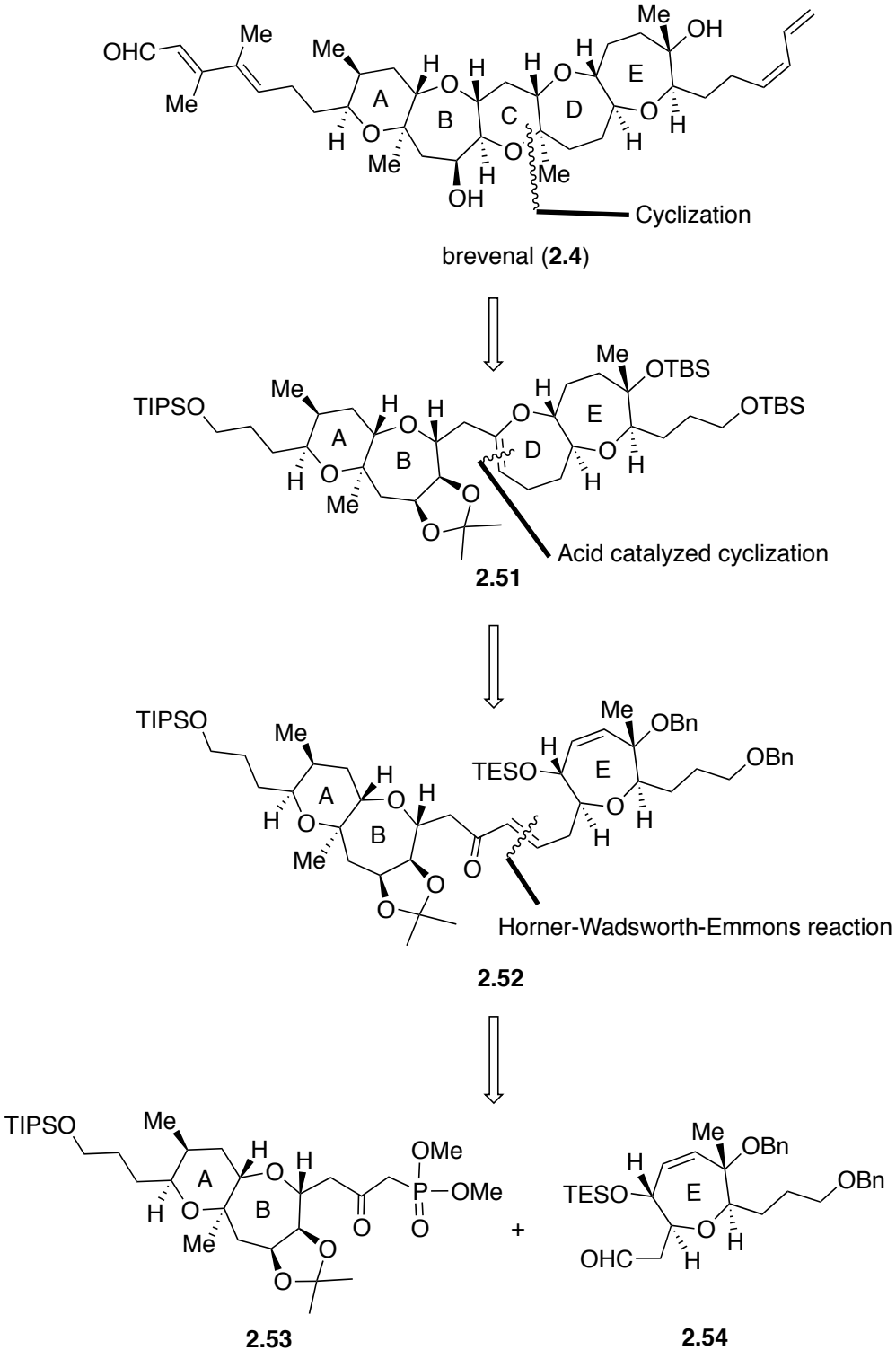


Figure 2.13. Crimmins' retrosynthetic analysis of brevenal

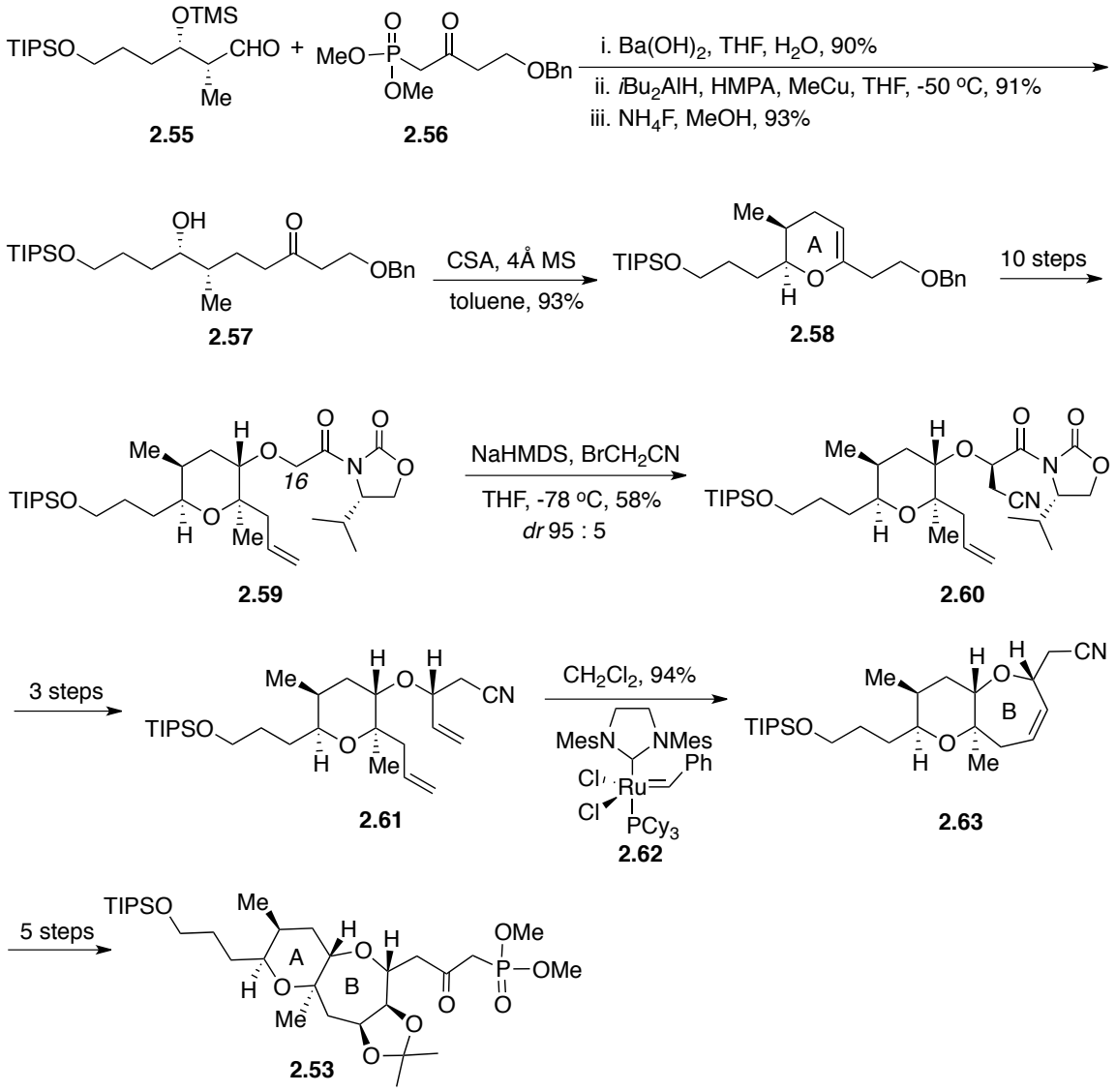


Figure 2.14. Crimmins' synthesis of the AB ring coupling partner **2.53**

catalyst **2.62**, diene **2.69** underwent ring-closing metathesis to afford the E ring of brevenal as nitrile **2.70**, from which the E ring coupling partner **2.54** was obtained in another four steps. The E ring aldehyde **2.54** was then successfully coupled with the AB ring phosphonate **2.53** under basic conditions to give α,β-unsaturated ketone **2.52**.

At this point of their synthesis, Crimmins and co-workers have demonstrated the power of their asymmetric glycolate alkylation/ring-closing metathesis methodology in

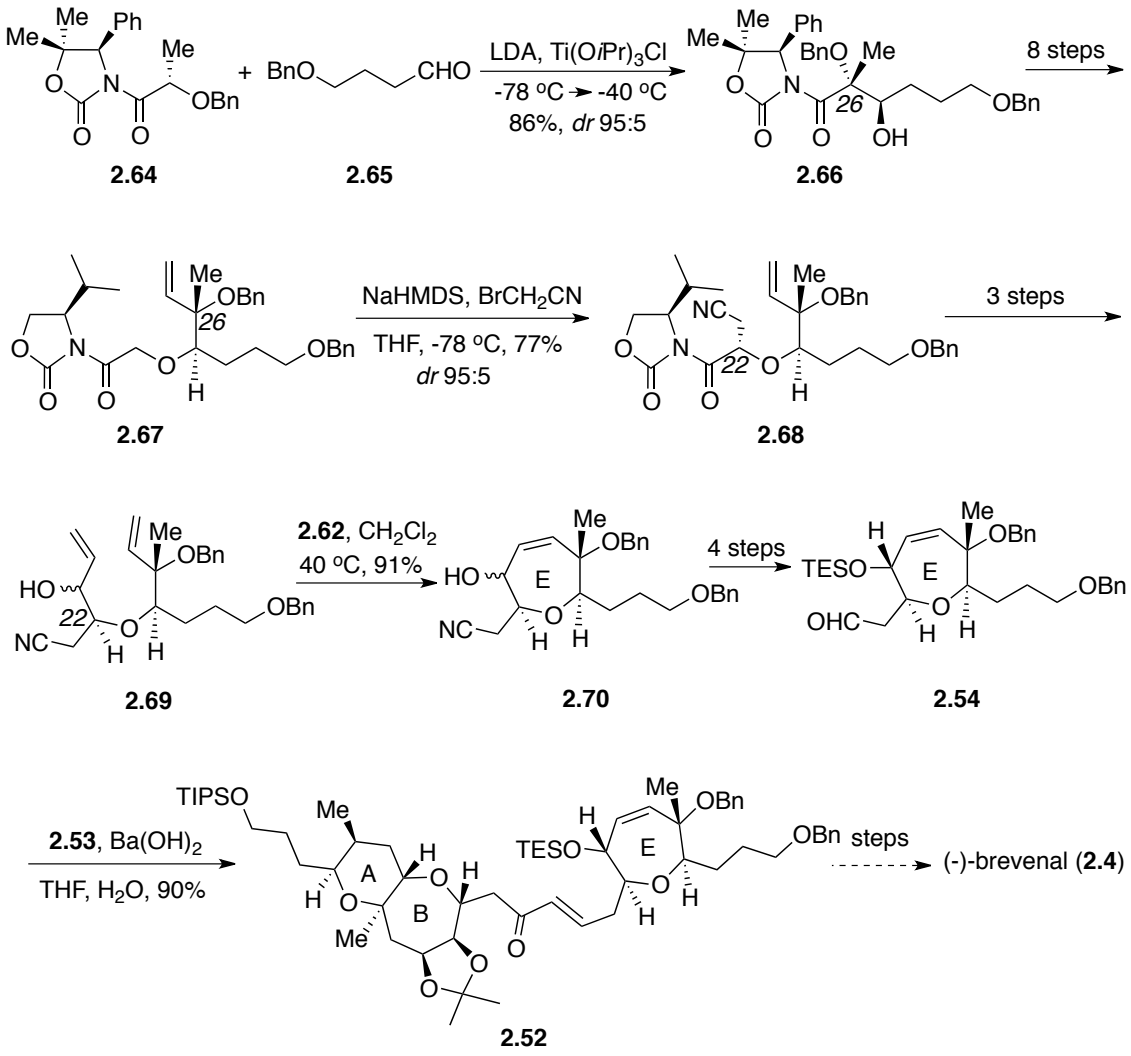


Figure 2.15. Crimmins' coupling between the AB ring and the E ring coupling partner

the construction of polycyclic ether architectures. Efforts to complete the total synthesis of brevenal using their convergent strategy are currently ongoing in their laboratory.

Results and Discussions

The unique structure and intriguing biological properties of brevenal (**2.4**) have prompted us to initiate a program towards its total synthesis. At the outset of our synthesis, we intended to adopt a highly convergent strategy that would not only supply

sufficient quantities of the natural product but also be amenable to synthesize analogues that could be used to further study the biological activities.

Our retrosynthetic analysis of brevenal (**2.4**) is shown in Figure 2.16. Central to our approach to brevenal was the convergent strategy that was previously described in Chapter 1 (Figure 1.21).[21] As in Sasaki and Kadota's syntheses, we planned to install the side chains at a late stage in the synthesis. The D ring of brevenal was envisioned to come from a reductive cyclization from the corresponding hydroxy ketone, which would be obtained from enol ether **2.72**. The C ring enol ether in turn was to be generated from an olefinic ester cyclization of ester **2.73**, which ultimately could be broken down to the AB ring alcohol **2.74** and the E ring acid **2.75**. We envisioned that both coupling precursors could be readily synthesized using our iterative cyclic enol ether/*C*-glycoside formation strategy depicted in Figure 1.2.

Synthesis of the AB Ring and the E Ring Coupling Precursors

The synthesis of the AB ring coupling partner **2.74** was designed and carried out by Dr. Karthik Iyer and Dr. John Rohanna from our group (Figure 2.17). From the TBDPS protected aldehyde **2.76**, a highly diastereoselective Brown crotylation with **2.77** afforded secondary alcohol **2.78**, which was subsequently protected as its PMB ether.[22] The two newly generated stereocenters would become the C8 and C9 of brevenal and would be used to control the formation of the remaining stereocenters in the AB ring precursor. A three-step alkene homologation involving hydroboration, oxidation, and Wittig olefination was then applied to **2.79** to afford alkene **2.80**. After removal of the PMB group, the resulting secondary alcohol **2.81** was coupled with known acid **2.82**[23]

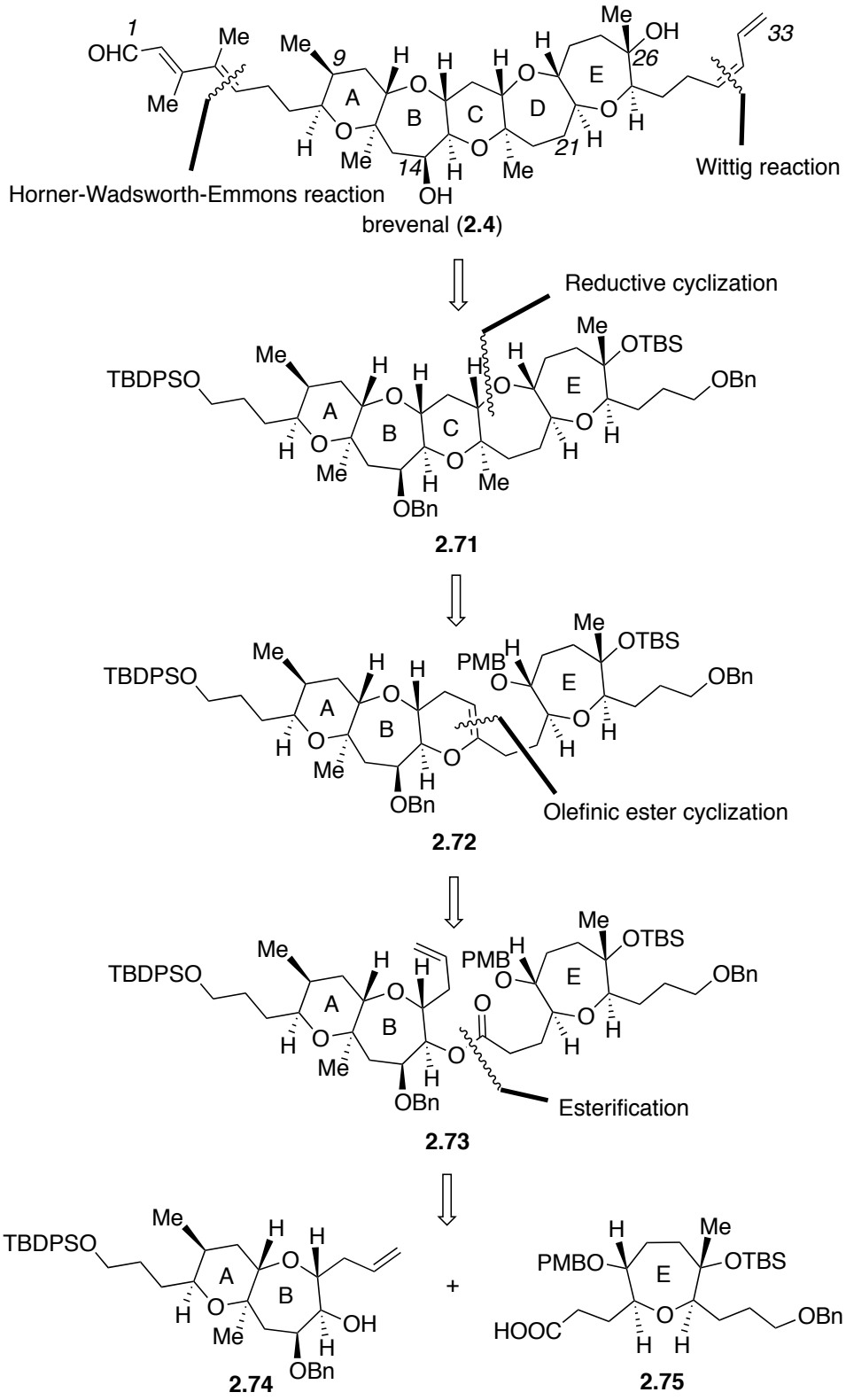


Figure 2.16. Retrosynthetic analysis of brevenal

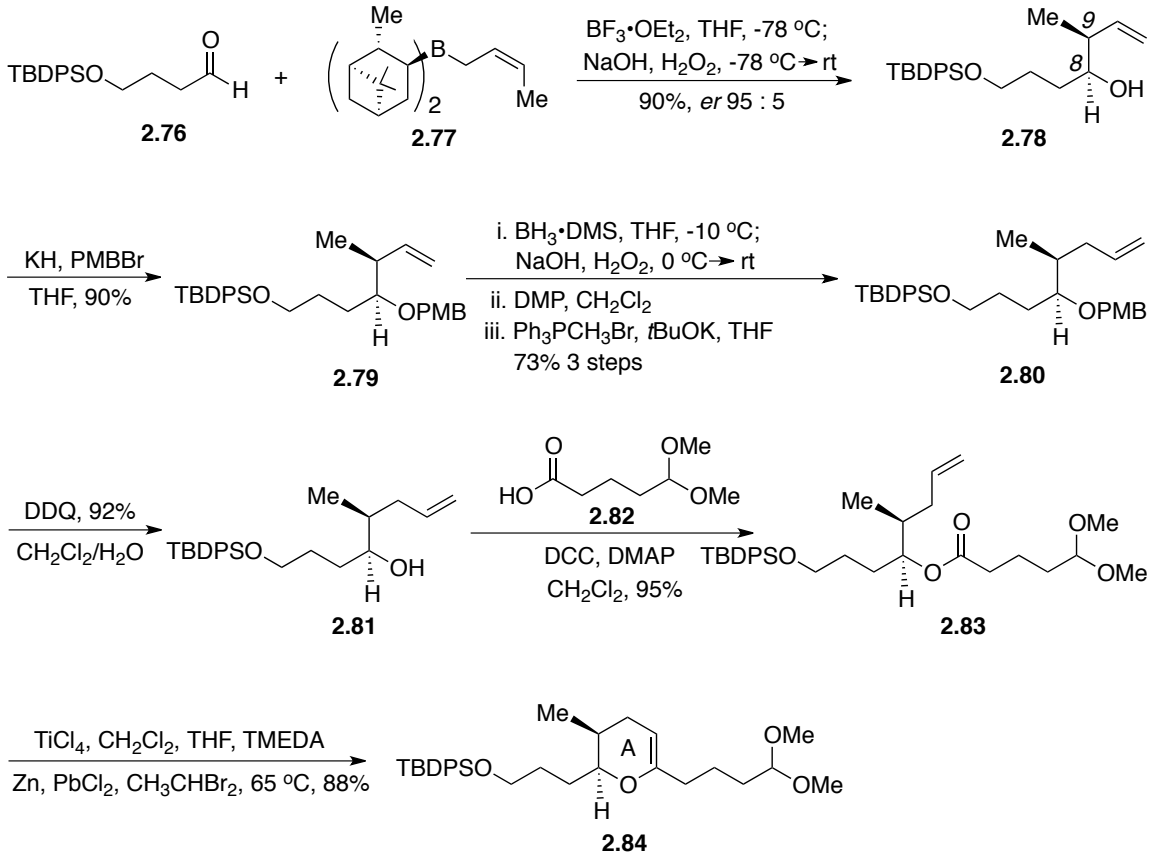


Figure 2.17. Synthesis of the A ring of brevenal

to provide olefinic ester **2.83**, which upon treatment with the reduced titanium ethylidene reagent, successfully furnished the A ring of brevenal as enol ether **2.84**.[24]

With the A ring enol ether in hand, a stereoselective oxidation with DMDO directed by the C9 methyl group afforded an epoxide, which upon in situ treatment with $AlMe_3$, underwent ring opening to give alcohol **2.85** as a single stereoisomer (Figure 2.18).[25] Using a two-step protocol involving the initial generation of a cyclic mixed acetal and subsequent elimination of methanol, hydroxy acetal **2.85** was converted into the B ring enol ether **2.86**.[26] From **2.86**, stereoselective epoxidation with DMDO directed by the C12 angular methyl group and subsequent ring opening with allyl Grignard reagent

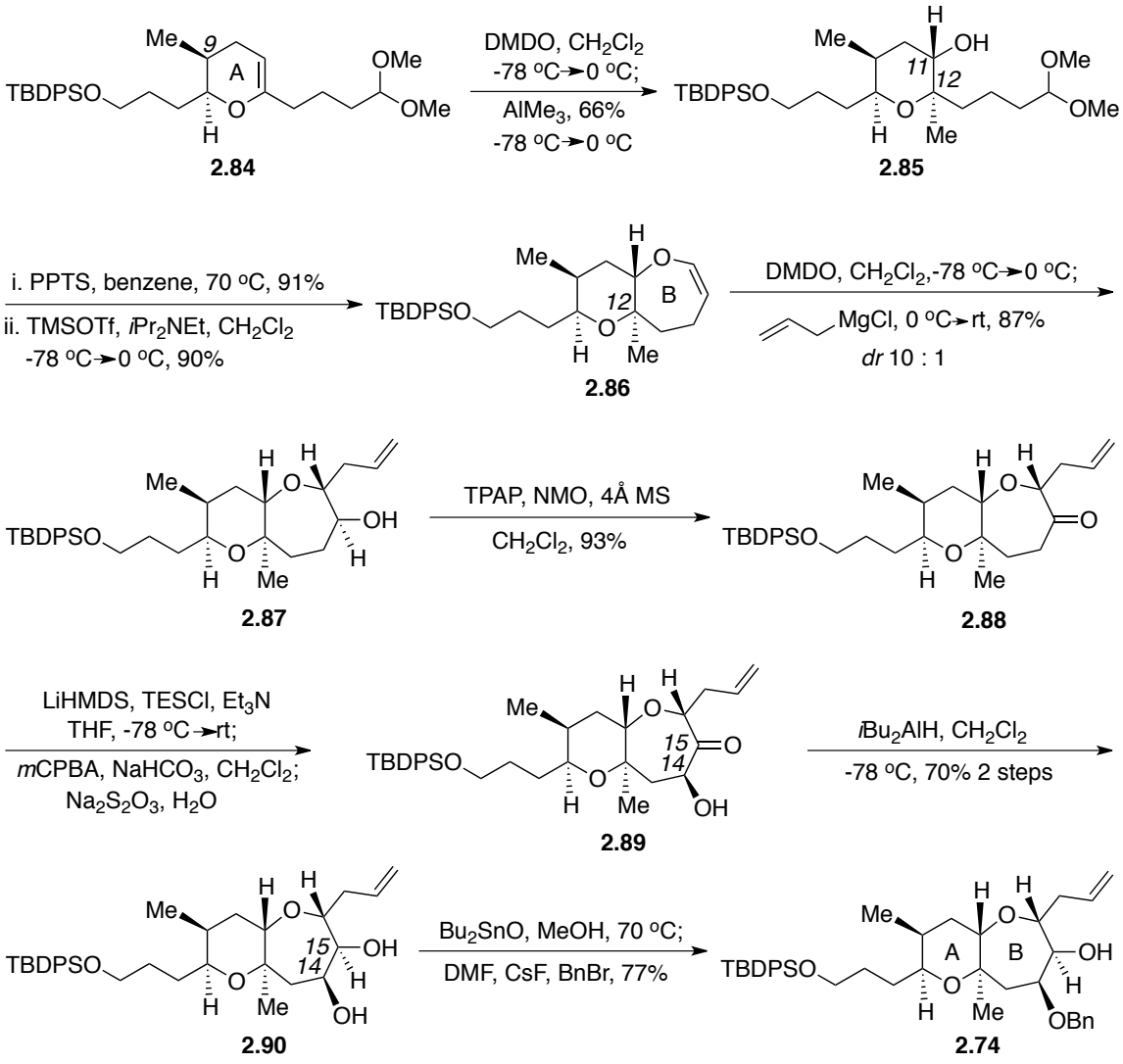


Figure 2.18. Synthesis of the AB ring coupling partner **2.74**

afforded secondary alcohol **2.87**.[27] After oxidizing **2.87** to the corresponding ketone **2.88**, a Rubottom oxidation was employed to stereoselectively install the C14 hydroxy group.[28] Reduction of the ketone in **2.89** in the presence of the C14 free alcohol gave diol **2.90** with the desired stereochemistry on C15.[13] The AB ring coupling partner **2.74** was finally obtained after selective protection of the sterically less hindered C14 hydroxy group as its benzyl ether.[29] As mentioned above, all of the stereocenters in **2.74** were

generated under substrate control once the C8 and C9 stereocenters had been established from the Brown crotylation reaction.

The synthesis of the E ring coupling partner **2.75** was designed and carried out by Dr. Jie Zhou from our group (Figure 2.19). The synthesis commenced from L-glyceraldehyde acetonide (**2.91**), whose only stereocenter would become the C22 of brevenal.[30] A chelation-controlled homoallylic Grignard reagent addition to the aldehyde afforded secondary alcohol **2.92**, which was then converted into **2.93** after deprotection of the acetonide and reprotection as a benzylidene acetal. Esterification of the secondary alcohol in **2.93** with acid **2.94**[31] afforded olefinic ester **2.95**, which when subjected to our modified Takai-Utimoto reaction conditions, succesfully gave the E ring of brevenal as enol ether **2.96**.

With the E ring enol ether in hand, oxidation with DMDO and in situ reduction of the resulting epoxide with *i*Bu_2AlH afforded alcohol **2.97** as a single diastereoisomer (Figure 2.20).[32] Oxidation and subsequent methyl Grignard addition gave tertiary alcohol

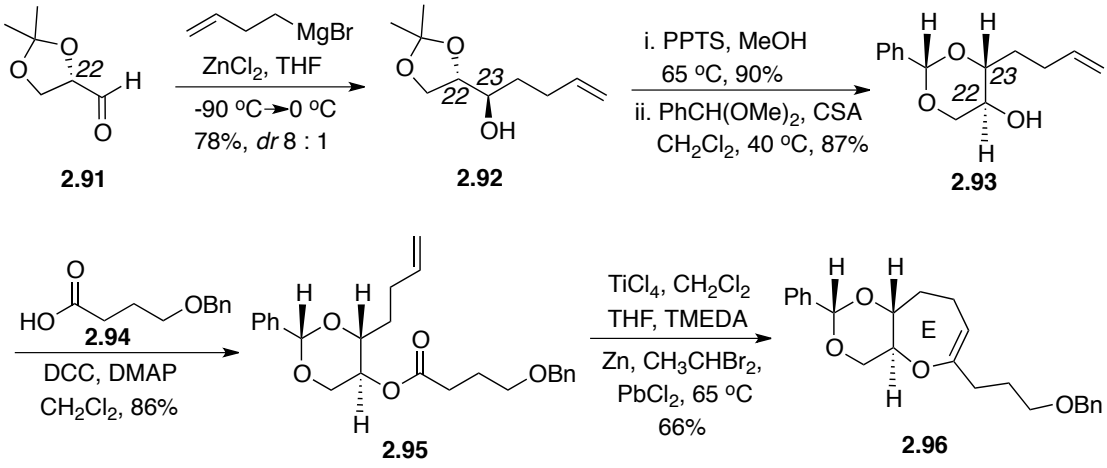


Figure 2.19. Synthesis of the E ring of brevenal

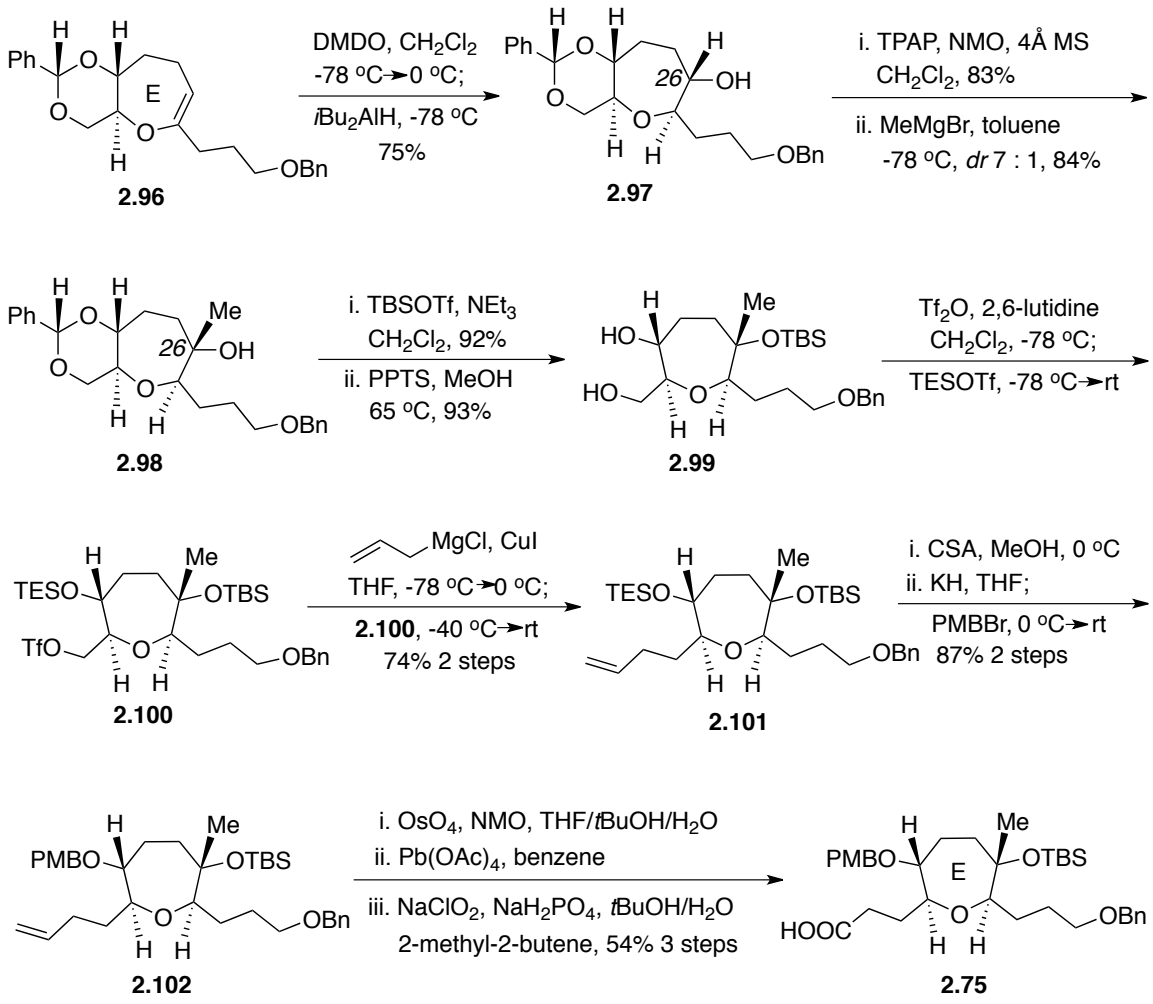


Figure 2.20. Synthesis of the E ring coupling partner **2.75**

2.98. After protecting the tertiary hydroxy group as a TBS ether, removal of the benzylidene protecting group afforded diol **2.99**, in which the primary alcohol was selectively converted into a triflate, and the secondary alcohol was protected as a TES ether. Allylcuprate addition to the triflate generated alkene **2.102** after protecting group manipulation. From **2.102**, the E ring coupling partner **2.75** was obtained after a three-step sequence involving dihydroxylation of the alkene, oxidative cleavage of the resulting diol, and Pinnick oxidation.[33]

Synthetic Efforts Towards Brevenal Pentacyclic Core

With both the AB ring and the E ring fragments in hand, we set out to study the coupling chemistry (Figure 2.21). Esterification between alcohol **2.74** and acid **2.75** proceeded smoothly under Yamaguchi's conditions to give olefinic ester **2.73**,[34] which when subjected to the modified Takai-Utimoto reaction conditions, successfully gave the six-membered C ring of brevenal as enol ether **2.72** in excellent yield.

With the C ring enol ether in hand, we were ready to functionalize the C ring and install the C19 angular methyl group, which in the retrosynthetic plan, could be realized using our DMDO oxidation and $AlMe_3$ addition protocol. We envisioned that the benzyl ether on C14 would control the facial selectivity in the process as was the case in our hemibrevetoxin B synthesis.[35] However, exposure of the resulting epoxide from the

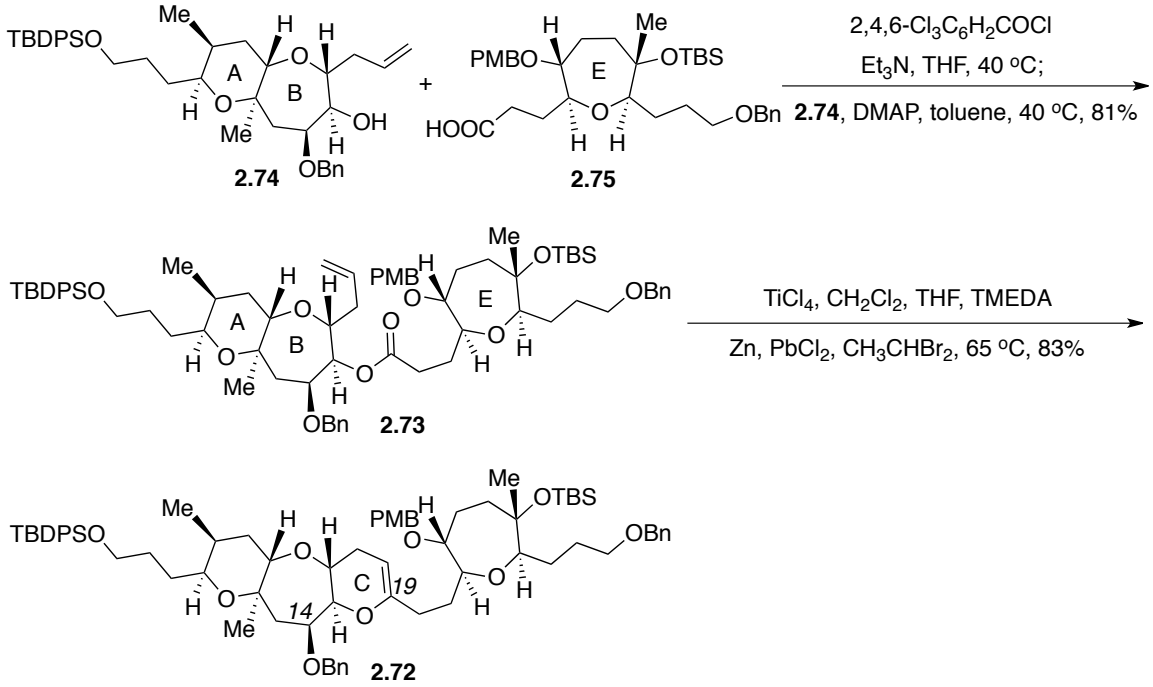


Figure 2.21. Coupling of the AB ring and the E ring fragments

DMDO oxidation of enol ether **2.72** to $AlMe_3$ resulted an inseparable 1.7:1 mixture of diastereomers at C18 and C19, which indicated a poor selectivity in the DMDO oxidation step (Figure 2.22).

To overcome the problem, we proposed that if we could exploit the formation of an oxocarbenium ion, the installment of the C19 methyl group should be decoupled from the selectivity of the epoxidation step because of the overwhelming propensity for axial addition of nucleophiles to oxocarbenium ions in six-membered rings.[36]

Dr. Jie Zhou from our group had developed a reaction system to generate α-*C*-glycosides using DMDO and organozinc reagents in the presence of TBSOTf or TESOTf.[37] In the example depicted in Figure 2.23, when the epoxide from enol ether **2.105** was exposed to TESOTf and $ZnMe_2$, *C*,*C*-ketal **2.108** was isolated as a 1.2:1 diastereomeric mixture at C8. The newly added methyl group on C9 occupied the axial

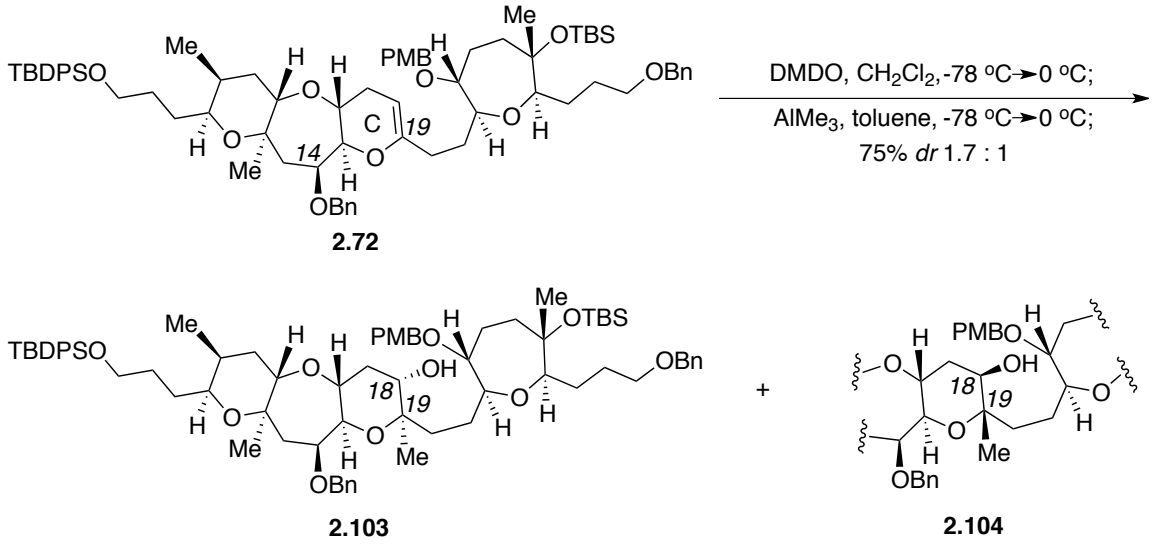


Figure 2.22. Efforts to install the C19 angular methyl group using DMDO and $AlMe_3$

position in both products, which was later proven through nOe studies after converting mixture **2.108** to ketone **2.109**. With this in mind, we subjected enol ether **2.78** to the same reaction condition. However disappointingly, the outcome from the treatment of the epoxide from **2.72** with TESOTf and $ZnMe_2$ was capricious, giving only trace amounts of the desired product **2.110** together with other unidentifiable materials and decomposition (Figure 2.24).

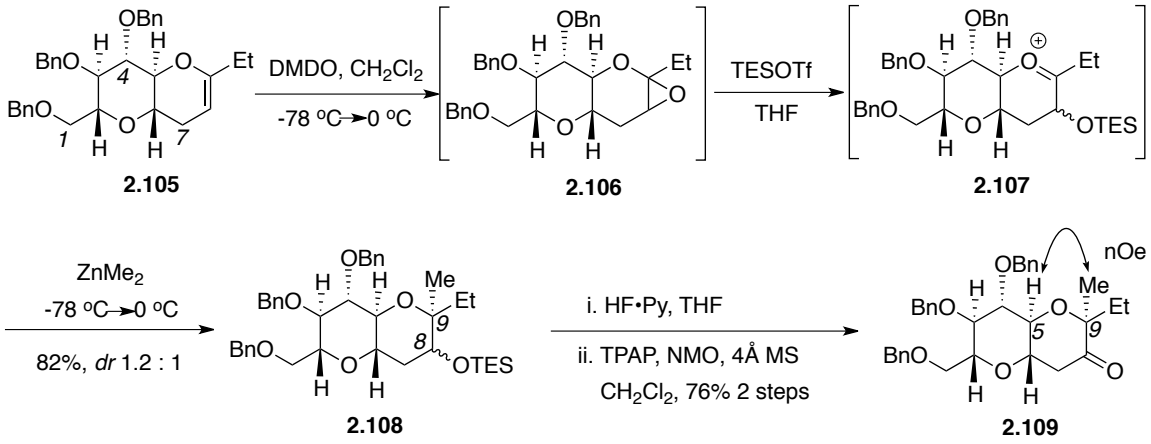


Figure 2.23. Axial methyl addition through an oxocarbenium ion

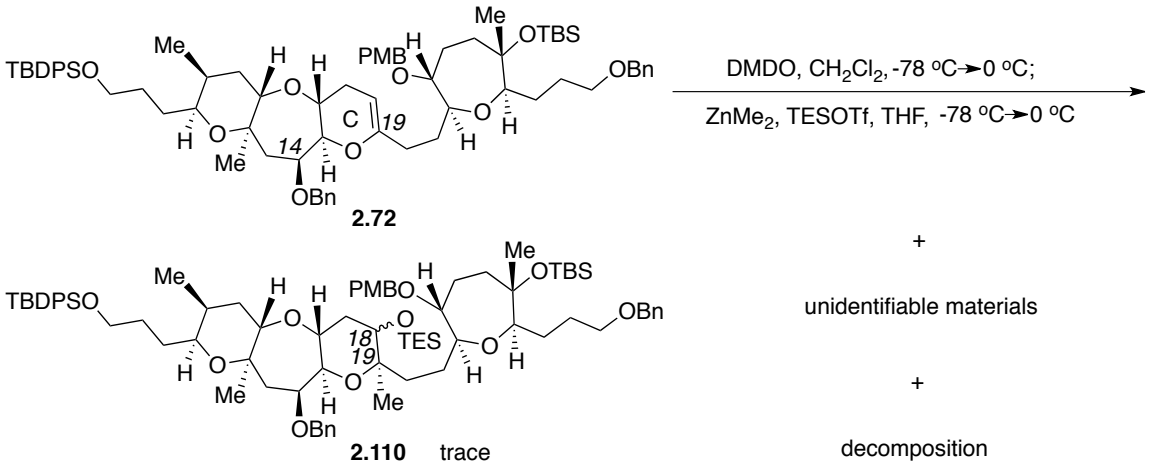


Figure 2.24. Efforts to install the C19 angular methyl group using oxocarbenium ion

The unsuccessful introduction of the C19 angular methyl group prompted us to examine a stepwise solution (Figure 2.25). In contrast to the result in Figure 2.22, treatment of the epoxide from **2.72** with EtSH and $Zn(OTf)_2$ afforded a 1.7:1 diastereomeric mixture of C18 secondary alcohols **2.111**.[19] After protecting the resulting hydroxy group as a TES ether, the stereoselective introduction of the C19 angular methyl group was finally accomplished using $ZnMe_2$ and $Zn(OTf)_2$ to give **2.112**.[17] Removal of

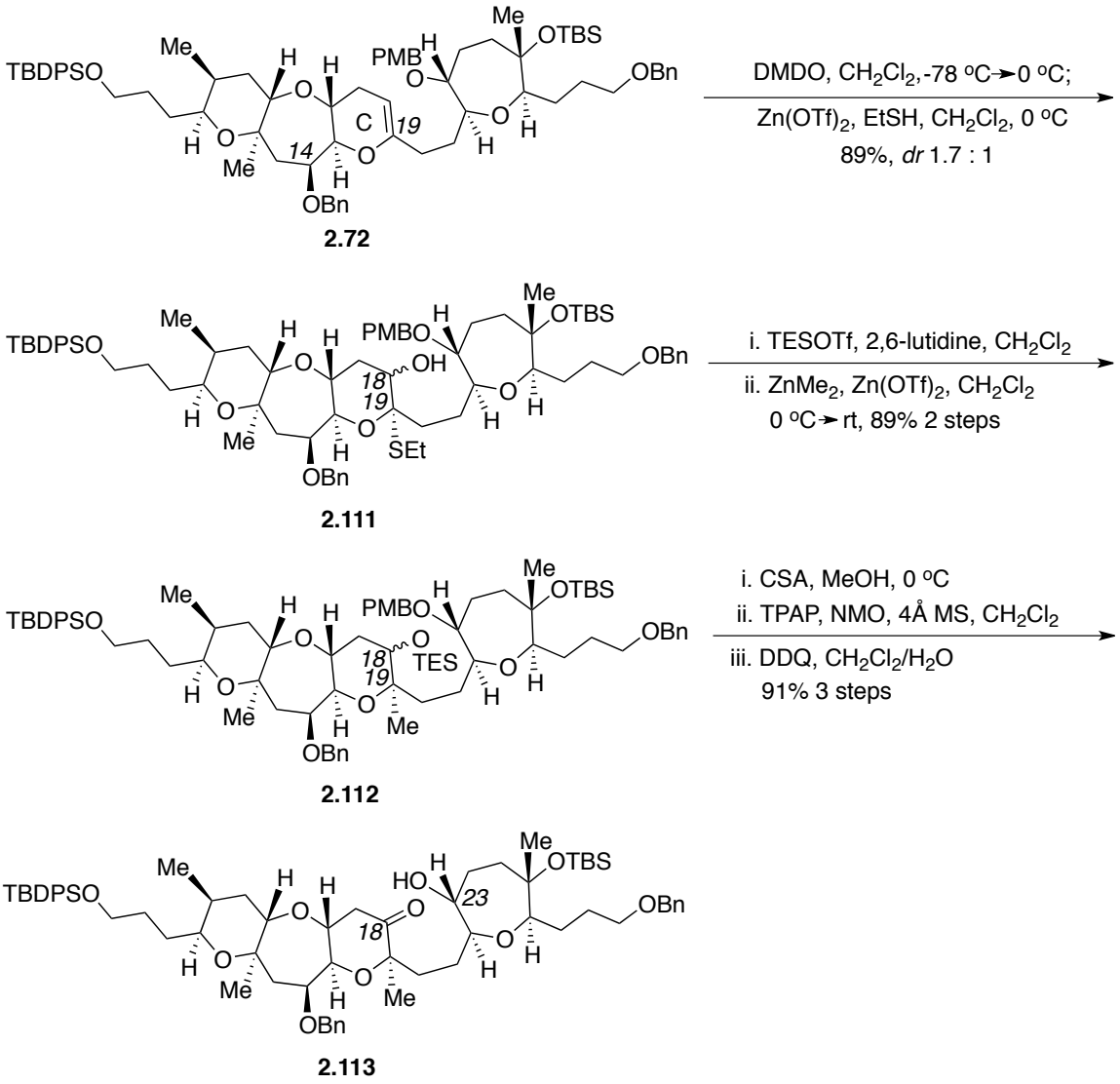


Figure 2.25. Installment of C19 angular methyl group using a stepwise strategy

the TES group, oxidation of the C18 alcohol, and removal of the PMB group afforded hydroxy ketone **2.113** as a single compound. It is noteworthy that **2.113** existed exclusively as the hydroxy ketone tautomer and not as the corresponding hemiketal, which later we realized was actually a harbinger of future problems with the cyclization to form the D ring.

As shown in our retrosynthetic analysis (Figure 2.16), the generation of the brevenal D ring from **2.113** required a reductive cyclization reaction. To this goal, **2.113** was subjected to Et_3SiH and Lewis acids. However, we were disappointed to find that the reaction resulted in complete decomposition of the starting material with no discernible product formation (Figure 2.26).

Other approaches to the D ring were also unsuccessful. First, a more conservative *O*,*S*-mixed ketal radical reduction approach was tested (Figure 2.27). Treatment of hydroxy ketone **2.113** with EtSH and $Zn(OTf)_2$ afforded the corresponding dithioketal, which was converted to *O*,*S*-mixed ketal **2.114** using a $AgClO_4$-promoted cyclization. Unfortunately, all attempts to reduce the mixed ketal or the corresponding sulfone under either homolytic or heterolytic conditions failed.

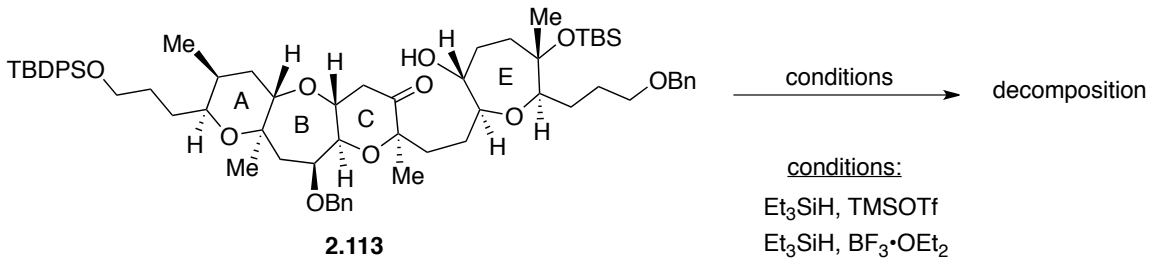


Figure 2.26. Efforts to form the D ring of brevenal using reductive cyclization

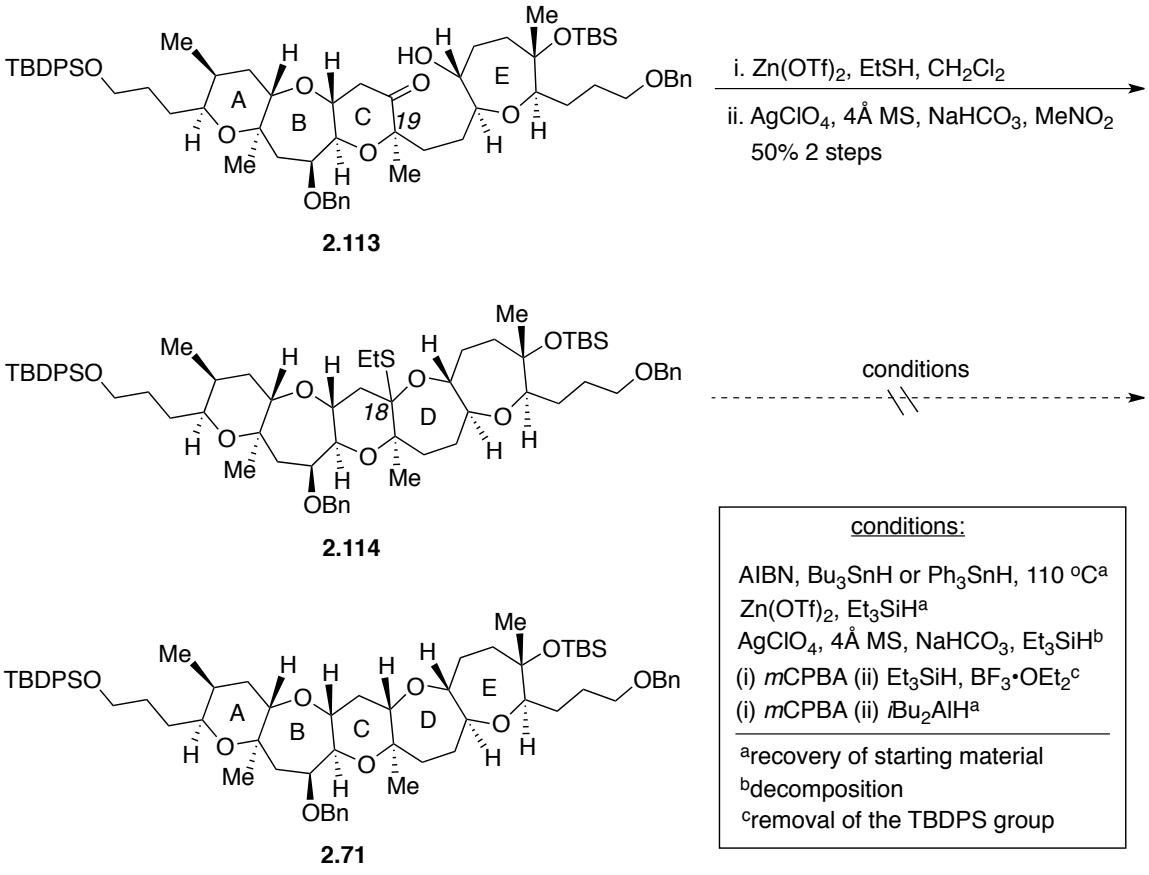


Figure 2.27. Efforts to form the D ring of brevenal through an *O*,*S*-mixed ketal

The studies outlined above suggested to us that the C19 angular methyl group in hydroxy ketone **2.113** was significantly inhibiting our efforts to the brevenal D ring. We attempted to solve this problem by turning our attention to the reductive cyclization of hydroxy ketone **2.116**, which had the alcohol and ketone functional groups at reversed positions compared to **2.113** (Figure 2.28). We envisioned that the sterically less hindered C23 ketone in **2.116** might facilitate the cyclization reaction. From the methyl addition product **2.115**, hydroxy ketone **2.116** was obtained after removal of the PMB group, oxidation, and removal of the TES group. In contrast to the two-step synthesis of *O,S*-mixed ketal **2.114** from hydroxy ketone **2.113**, treatment of hydroxy ketone **2.116**

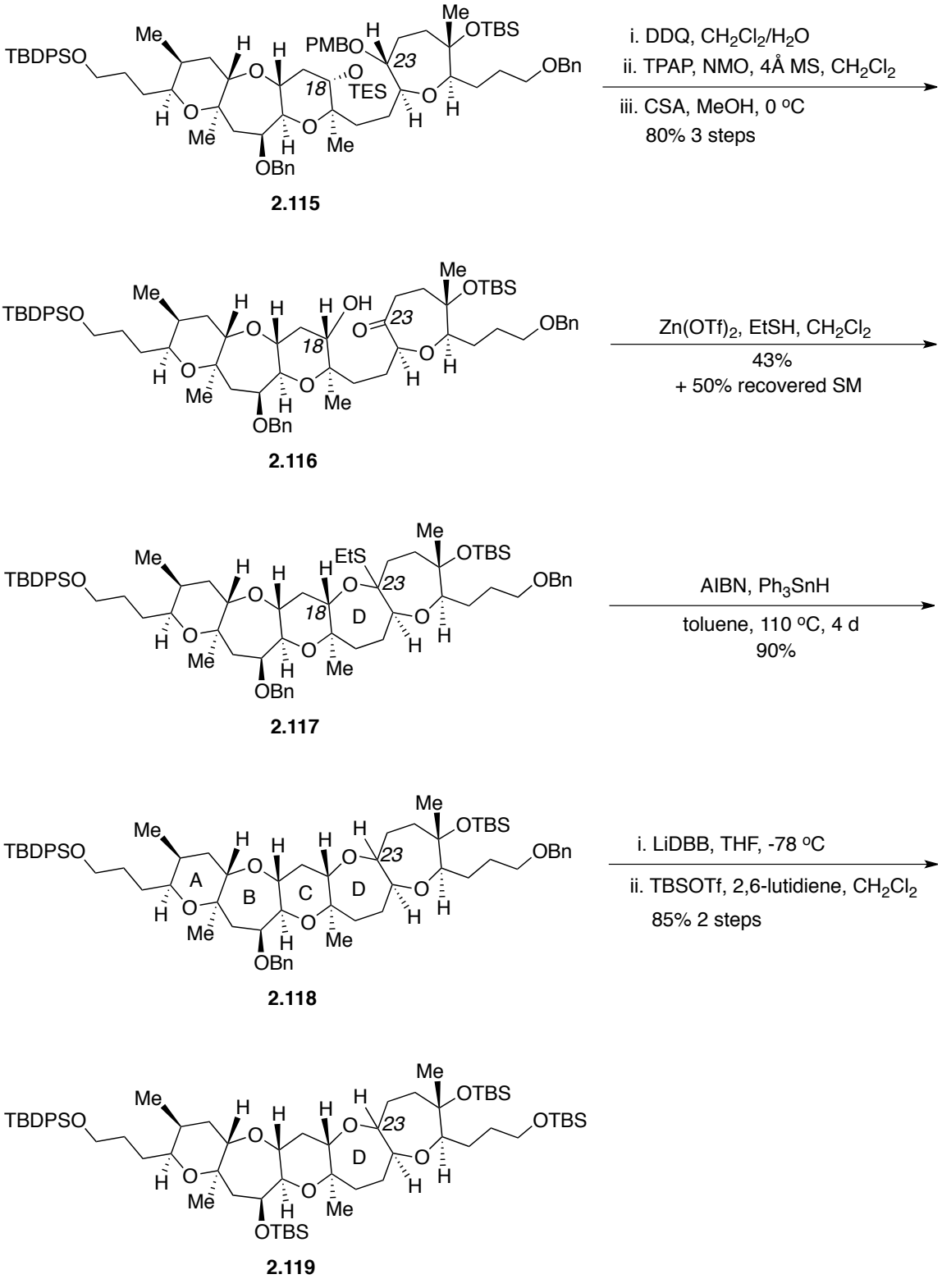


Figure 2.28. Efforts to synthesis the brevenal pentacyclic core

with $Zn(OTf)_2$ and EtSH gave *O,S*-mixed ketal **2.117** directly. More interesting was that the radical reduction of **2.117** with AIBN and Ph_3SnH successfully afforded oxepane **2.118** as a single stereoisomer after 4 days in refluxing toluene. Removal of the benzyl groups in **2.118** followed by TBS ethers formation gave **2.119**, a known intermediate in Sasaki's total synthesis of brevenal.[13] Unfortunately, although the mass spectroscopy data for **2.119** was correct, the ^1H NMR data did not match that previously reported by Sasaki. Although not definitively established, we presume that pentacycle **2.119** differs from the brevenal core at C23.

Successful Synthesis of Brevenal Pentacyclic Core

While our unsuccessful efforts to the brevenal core from **2.113** and **2.116** were disappointing, we realized that we could easily modify our synthetic plan by switching the acid/alcohol coupling partners. Thus, a new retrosynthetic analysis was proposed with AB ring fragment **2.123** being the acid coupling partner and E ring fragment **2.124** being the alcohol coupling partner (Figure 2.29). In the new strategy, the seven-membered D ring was envisioned to come from olefinic ester cyclization, which would certainly be more challenging than the analogous reaction in the previous route to form the six-membered C ring. But on the other hand, we envisioned that the late-stage cyclization to form the C ring and installation of the C19 angular methyl group would help us overcome some of the problematic transformations in our previous efforts.

With the new synthetic strategy in mind, the revised AB ring coupling partner **2.123** was synthesized from the previous intermediate **2.90** in four steps (Figure 2.30). After protecting the two hydroxy groups in **2.90** as TES ethers, the acid coupling partner

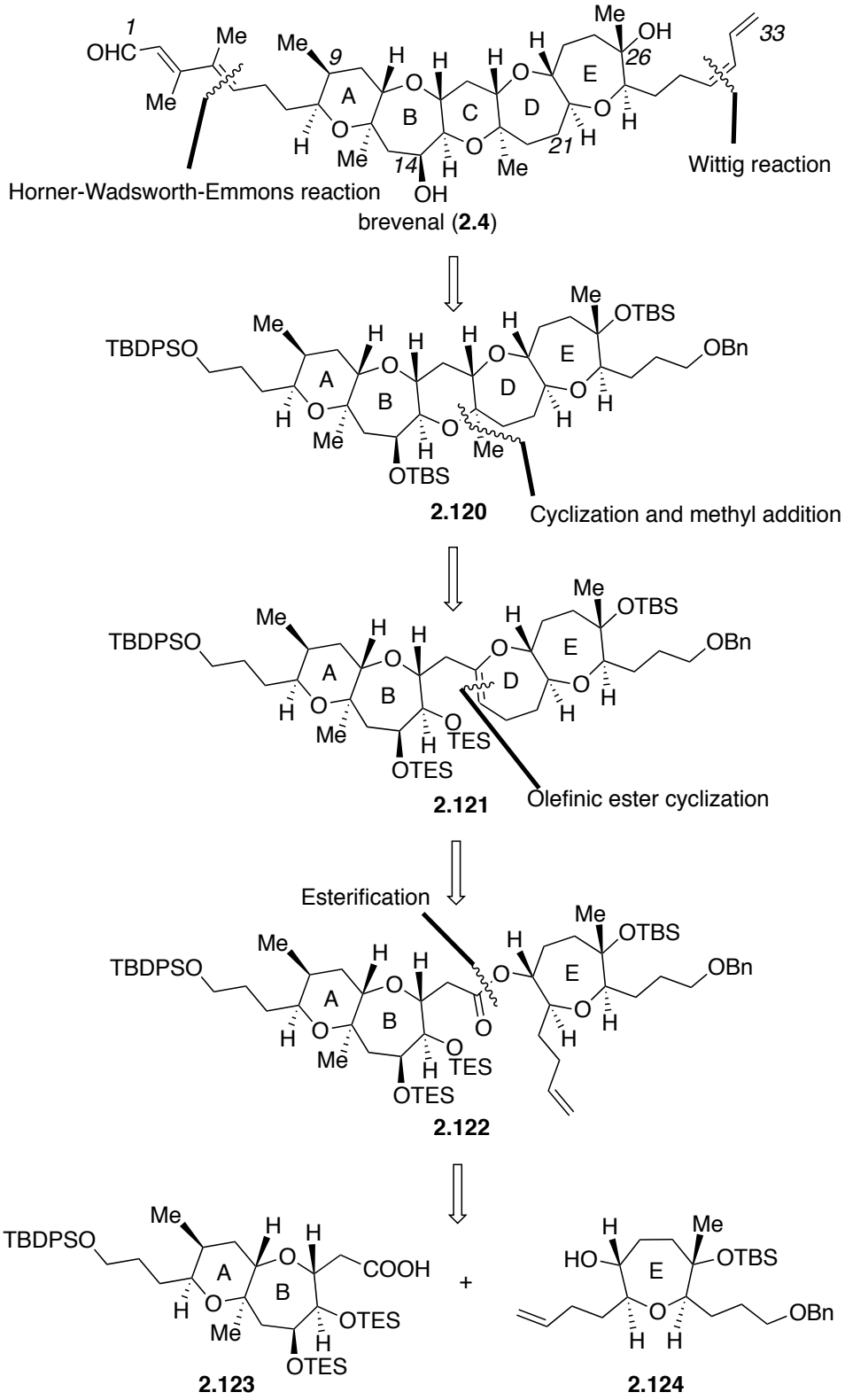


Figure 2.29. Revised retrosynthetic analysis of brevenal

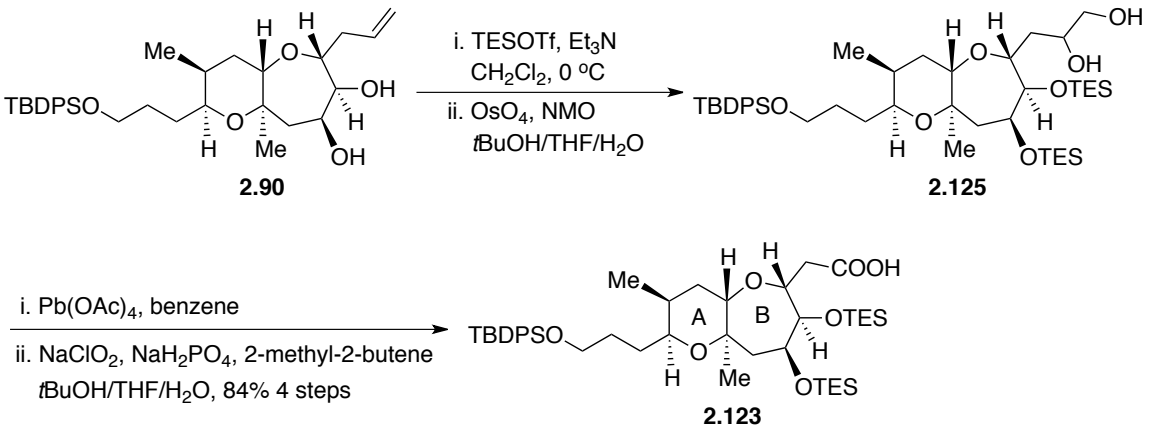


Figure 2.30. Synthesis of the AB ring coupling partner **2.123**

2.123 was obtained after a three-step sequence involving dihydroxylation of the alkene, oxidative cleavage of the resulting diol, and Pinnick oxidation. The new E ring coupling partner **2.124** itself was a previously used intermediate in Figure 2.20.

With both coupling partners in hand, we set out to study the new strategy (Figure 2.31). Esterification of acid **2.123** with alcohol **2.124** was accomplished using Shiina's conditions to give ester **2.122**.[38] Yamaguchi esterification was not as effective for this specific reaction. After optimization of the olefinic ester cyclization conditions, we were pleased to find that the desired D ring enol ether **2.121** was generated in 30% yield from ester **2.122** along with 70% acyclic enol ether **2.126**. Fortunately, the acyclic material **2.126** could be converted into **2.121** using Grubbs 2nd generation catalyst **2.62** under an ethylene atmosphere in refluxing benzene. This gave an additional 42% of cyclic materials consisting of a 5:1 mixture of **2.121** and the corresponding dihydropyran from alkene isomerization under metathesis conditions. Thus, the D ring enol ether **2.121** could be obtained in 65% overall yield from olefinic ester **2.122**.

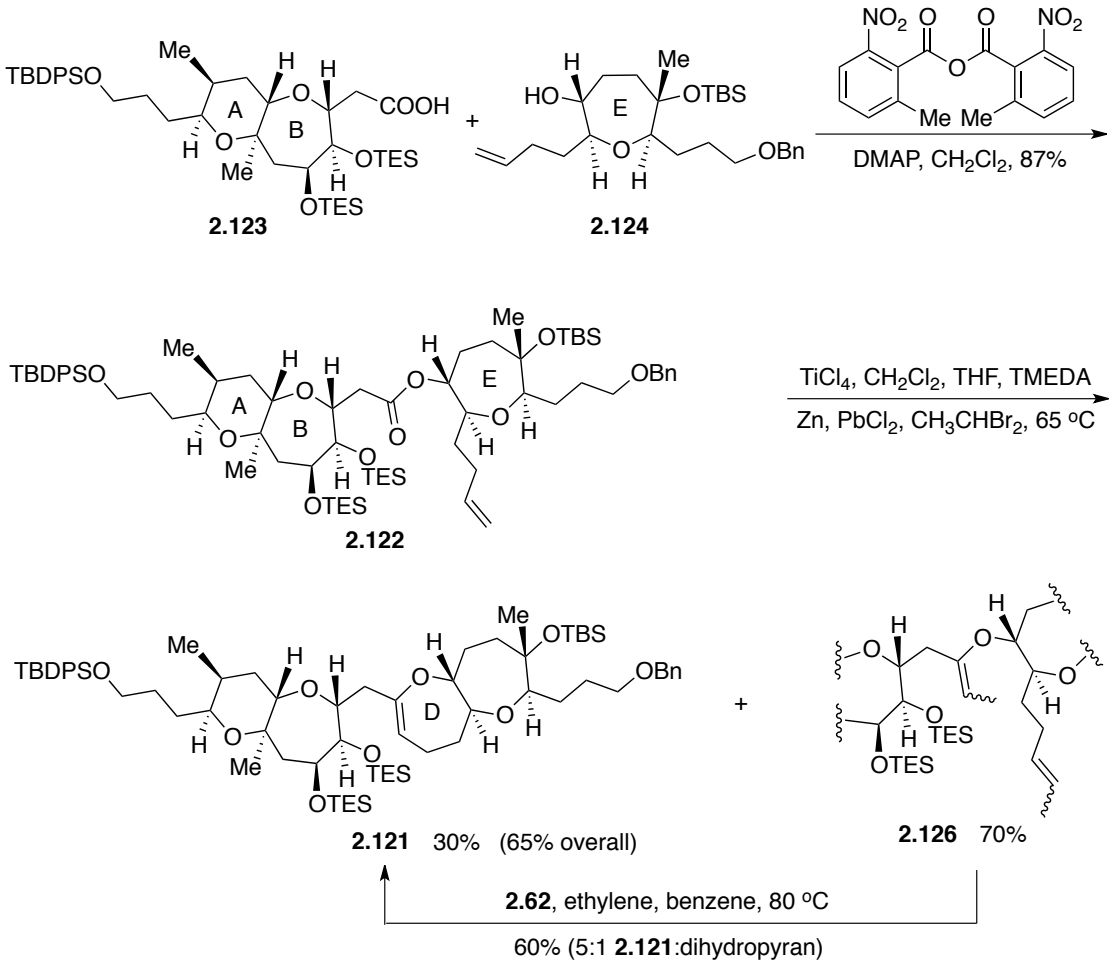


Figure 2.31. Synthesis of D ring of brevenal using olefinic ester cyclization

With the D ring in hand, oxidation of the enol ether in **2.121** with DMDO and in situ reduction of the resulting epoxide using *i*Bu_2AlH afforded secondary alcohol **2.127** in 75% yield (Figure 2.32). In sharp contrast to the DMDO oxidation of the six-membered C ring enol ether **2.72** (Figure 2.22), alcohol **2.127** was obtained as a single stereoisomer, which indicated that the DMDO epoxidation of **2.121** was stereoselective. Based on DFT calculations in a model oxepene, we believe that the high stereoselectivity in the generation of the C18 stereocenter is a result of unfavorable torsional interactions between the C20 pseudoaxial hydrogen atom and DMDO during the transition state.[32]

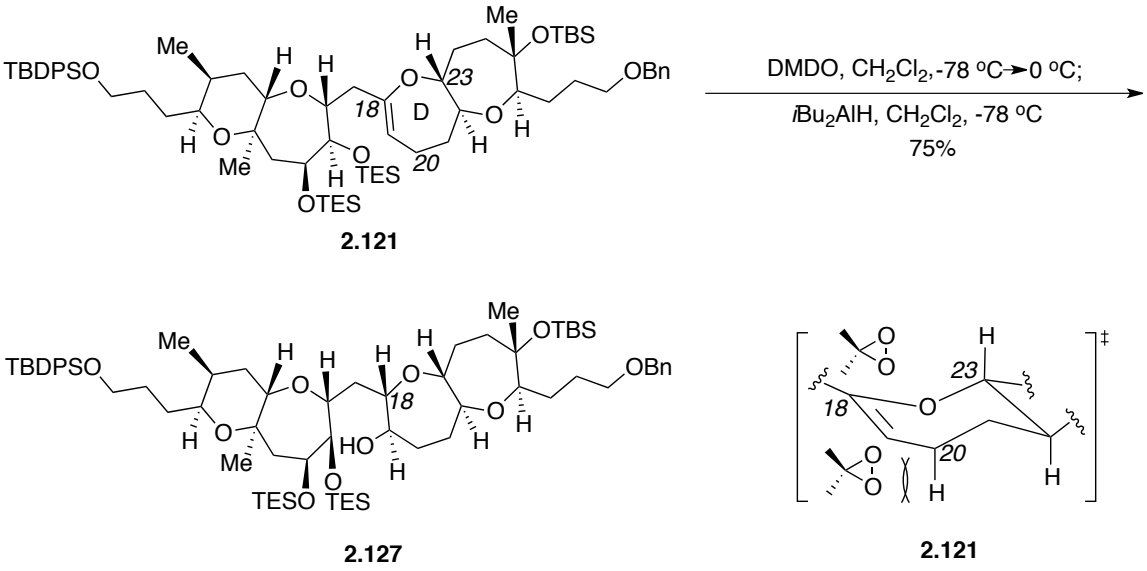


Figure 2.32. Formation of the C18 stereocenter

With the C18 stereocenter successfully set, we were ready to generate the brevenal C ring. Oxidation of secondary alcohol **2.127** using Ley's conditions gave ketone **2.128**, which intercepted Sasaki's total synthesis of brevenal (Figure 2.33). All the spectral data (^{1}H, ^{13}C, IR, MS, $[\alpha]^{20}_D$) matched that reported previously.[13] To complete the synthesis of brevenal pentacyclic core, ketone **2.128** was subjected to $Zn(OTf)_2$ and EtSH, which removed both TES groups and successfully promoted cyclization to generate *O*,*S*-mixed ketal **2.129**. After protecting the remaining C14 hydroxy group as a TBS ether, Sasaki had installed the C19 methyl group with a two-step protocol using *m*CPBA and subsequent treatment of the resulting sulfone with $AlMe_3$. We found the more direct $ZnMe_2$ and $Zn(OTf)_2$ protocol was equally effective to install the C19 methyl group to furnish the brevenal pentacyclic core as **2.120**.[17]

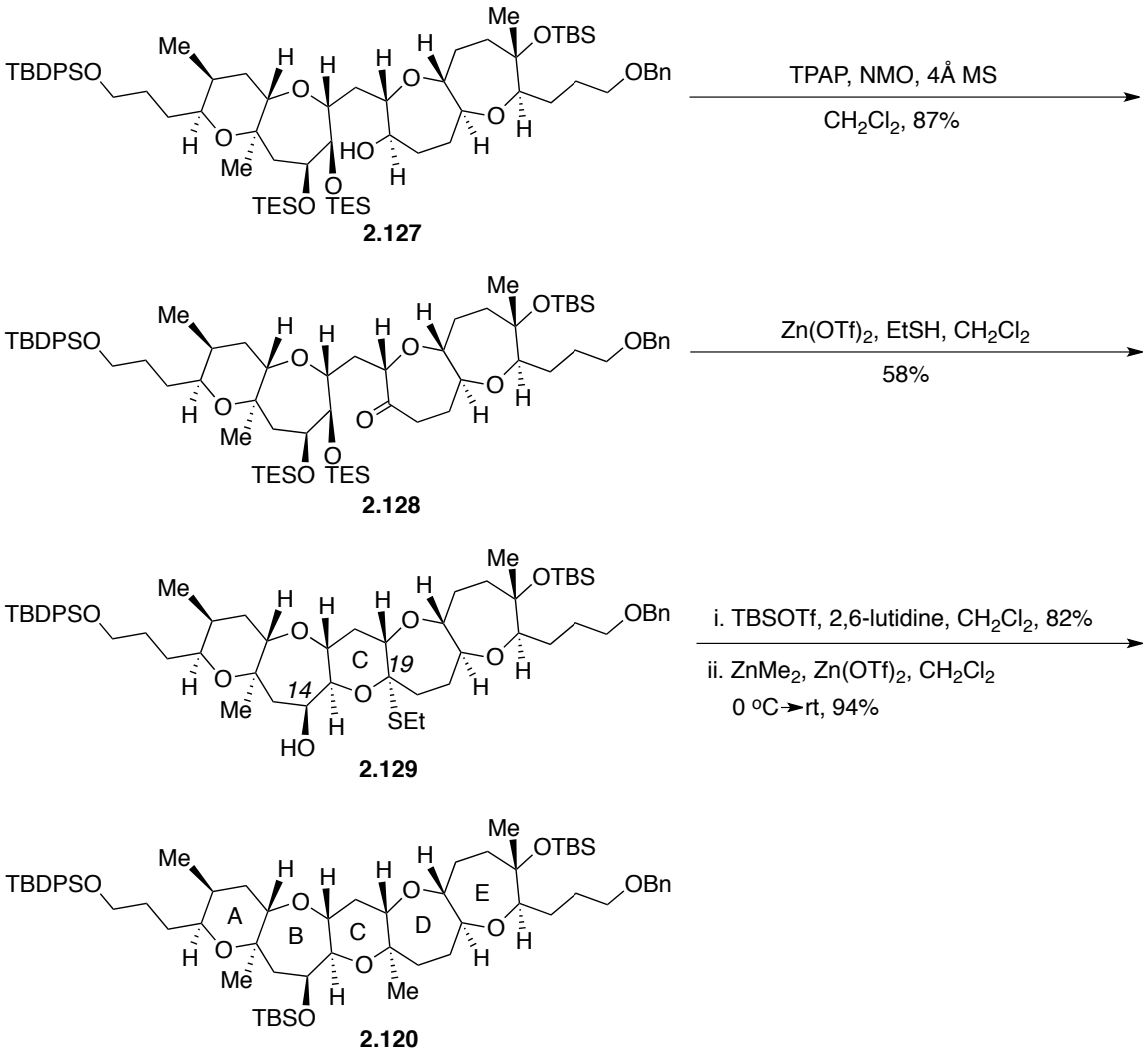


Figure 2.33. Synthesis of the brevenal pentacyclic core **2.120**

Completion of the Total Synthesis of Brevenal

With the pentacyclic core structure **2.120** in hand, we were finally prepared to finish the total synthesis of brevenal (Figure 2.34). To this goal, a modified Kadota end game protocol was employed to install the two side chains.[16] The E-ring side chain incorporation started with deprotection of the C30 benzyl group, which was effected using hydrogenolysis in Kadota's synthesis. In our hands, reductive deprotection with LiDBB was more effective than the use of Pd/C and H_2 to give the corresponding primary

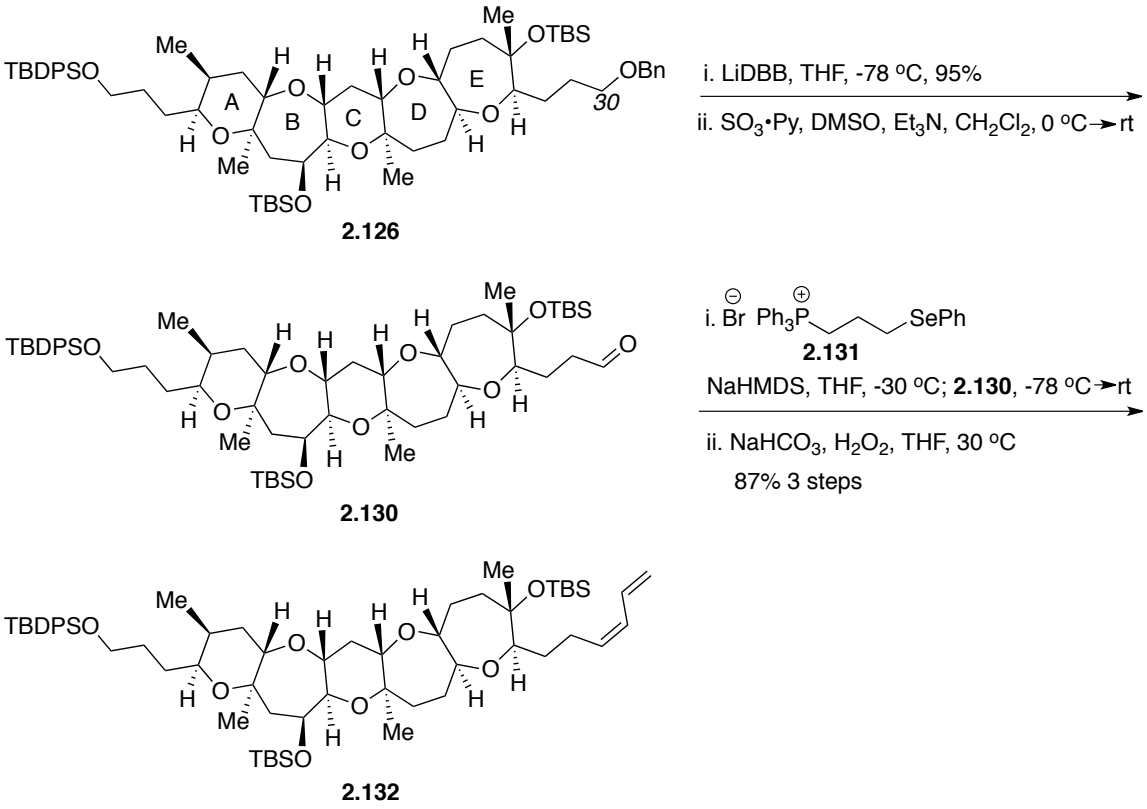


Figure 2.34. Installment of the E-ring side chain

alcohol. The alcohol was subsequently converted to aldehyde **2.130** using a Parikh-Doering oxidation.[39] Wittig coupling using phosphonium salt **2.131** and NaHMDS followed by oxidative elimination of the phenyl selenoxide successfully afforded (*Z*)-diene **2.132**, thus completing the E-ring side chain of brevenal.[40]

The installment of the A-ring side chain started with the selective deprotection of the primary TBDPS group in the presence of two TBS groups using HOAc and TBAF to give **2.133** (Figure 2.35).[41] The resulting primary alcohol was oxidized to give aldehyde **2.134**, which following a Horner-Wadsworth-Emmons reaction with the lithium salt of phosphonate **2.135** successfully afforded the desired (*E,E*)-diene **2.136**. From the same compound **2.136**, Kadota had completed their total synthesis of brevenal after reduction

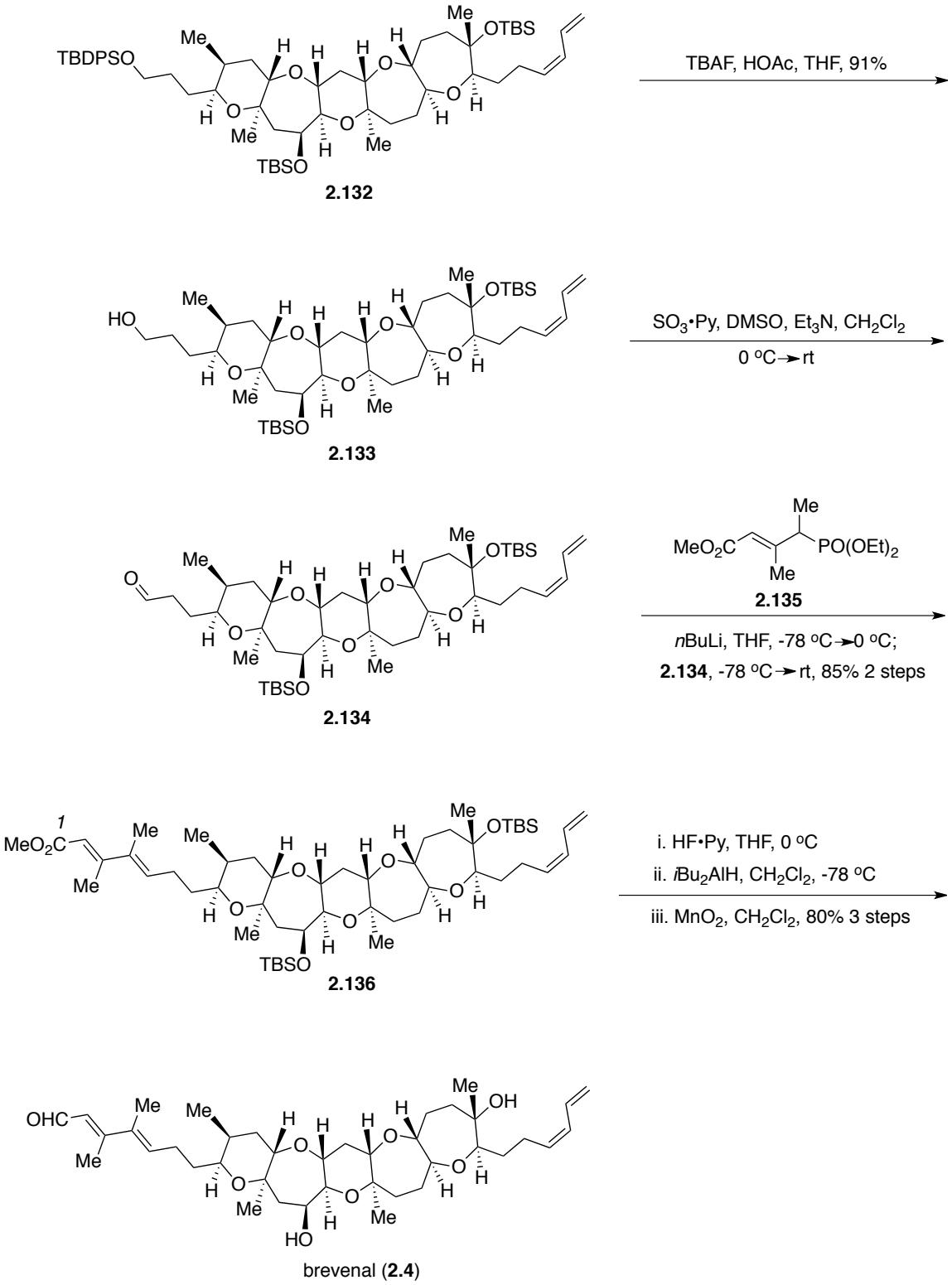


Figure 2.35. Completion of the total synthesis of brevenal (**2.4**)

of the ester with *i*Bu_2AlH, removal of the TBS groups using TBAF, and selective oxidation of the C1 allylic alcohol. However in our hands, the allylic alcohol obtained after the first two steps was unstable to the chromatography that was required after TBAF deprotection. So we adopted a slightly different protocol to finish our total synthesis of brevenal. The two TBS groups were first removed using HF•Py, and the resulting diol was subjected to *i*Bu_2AlH to afford the corresponding allylic alcohol, which, without the need for chromatography, was directly oxidized to brevenal (**2.4**) using MnO_2. Our spectral data for brevenal matched that previously reported.[2d]

Thus, we have accomplished the total synthesis of brevenal (**2.4**) in 38 steps (longest linear sequence, 28 steps to the pentacyclic core) in 0.99% overall yield. Our work compared favorably to the other total syntheses of brevenal where the Sasaki group required 65 steps with a 0.26% overall yield and the Kadota group required 57 steps with a 0.84% overall yield.

After our successful total synthesis of brevenal, we also synthesized an analogue of brevenal (**2.139**) from the pentacyclic intermediate **2.120** (Figure 2.36). Both compounds were sent to our collaborators for biological evaluation. The preliminary data have demonstrated that both brevenal and the analogue produce a concentration-dependent antagonism of the brevetoxin B-induced calcium influx in mouse cerebral cortical neurons. Interestingly, the analogue is shown to be ten times more potent than brevenal in this assay. The concentration-dependent antagonism is presumably through an inhibition of the binding of brevetoxin B to VGSC by brevenal and the analogue. Further biological tests are currently underway to elucidate the exact mechanism of this antagonism.

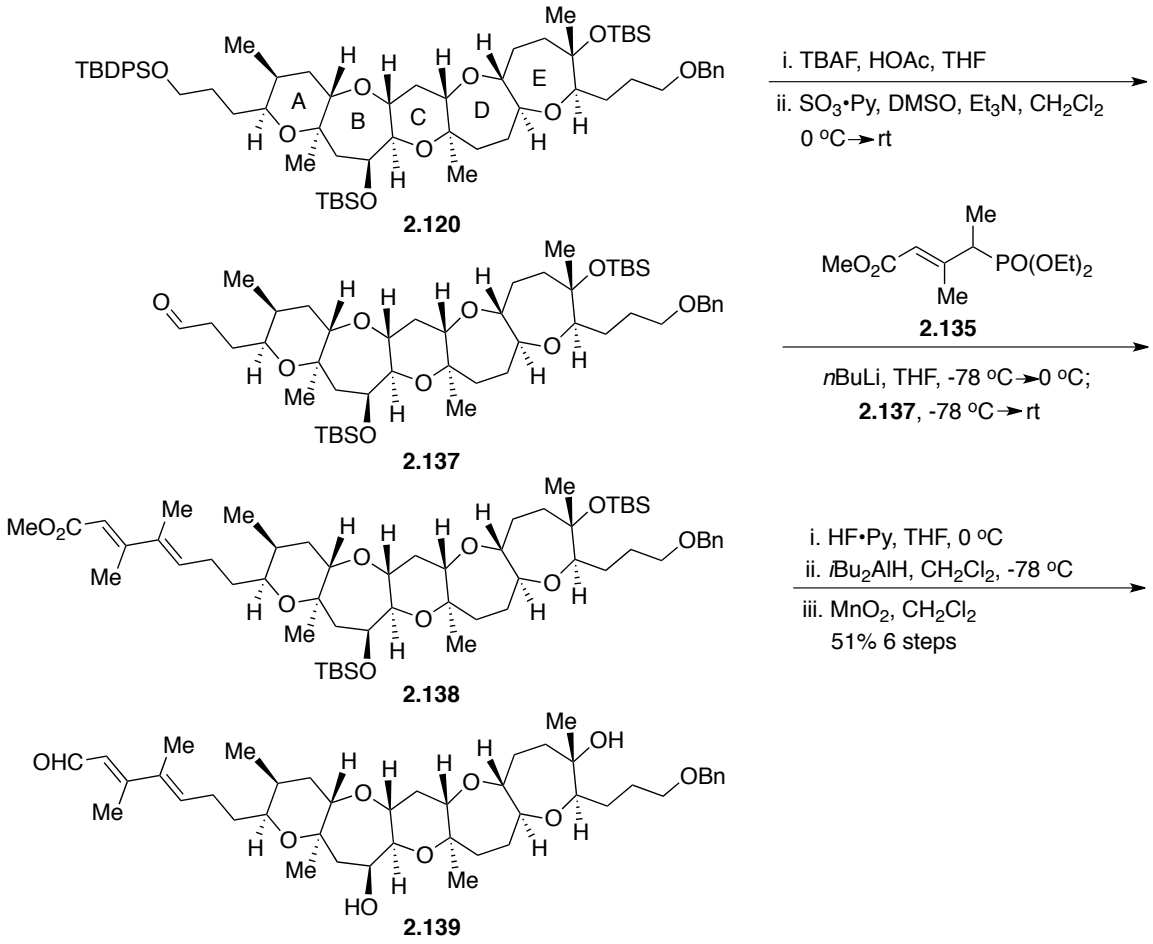


Figure 2.36. Synthesis of brevenal analogue **2.139**

Conclusion

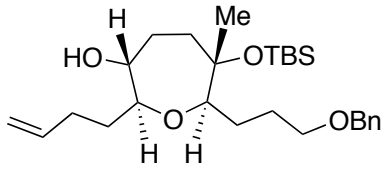
To summarize, we have achieved the total synthesis of brevenal utilizing our olefinic ester cyclization strategy to both build the individual AB and E ring fragments and to carry out their convergent coupling. Our flexible coupling strategy has allowed us to readily modify the coupling partners to accommodate the specific requirements in the synthesis. We are currently in collaboration with Prof. Thomas Murray at Creighton University to further investigate brevenal's biological properties and its inhibition of the binding of the brevetoxins to VGSC.

Experimentals

NMR spectra were recorded on Varian Inova-400 MHz, Varian Inova-500 MHz or Varian VXR-500 MHz spectrometers. Chemical shifts were reported in δ, parts per million (ppm), relative to benzene (7.16), chloroform (7.27), or dichloromethane (5.32) as internal standards. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass spectrometer. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Optical rotations were obtained on a Perkin-Elmer Model 343 polarimerter (Na D line) using a microcell with 1 dm path length. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin: Oxford, 1966). Dichloromethane, 2,6-lutidine, triethylamine, TMEDA, chlorobenzene and pyridine were distilled from CaH_2. Tetrahydrofuran and diethyl ether were dried from the sodium ketyl of benzophenone and distilled before use. Zinc dust (<10 μm, Aldrich) was activated by washing with 5% hydrochloric acid, H_2O, methanol, and ether and dried in vacuo overnight. All other reagents were used without further purification. Unless otherwise noted, all reactions were performed under a nitrogen atmosphere in flame-dried glassware using standard syringe, cannula, and septa apparatus. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20mm Hg). Analytical thin–layer chromatography (TLC) was performed on silica gel plates (0.25 mm) precoated with a fluorescent indicator. Flash chromatography was performed using 40–63 μm silica gel (200 X 400 mesh).

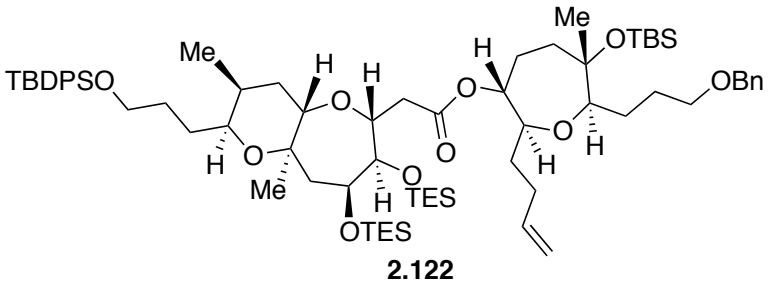
Procedures and Characterizations

The characterization and procedures for compounds **2.101**, and **2.123** were previously reported.[37,42]



2.124

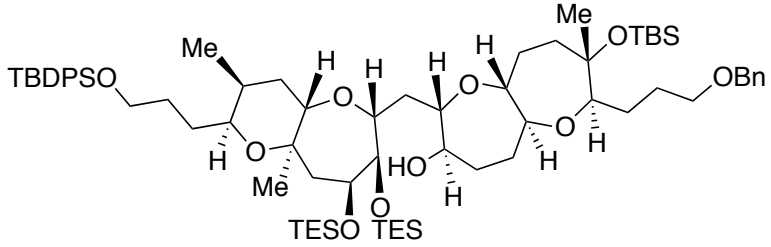
Preparation of alcohol 2.124. To a solution of **2.101** (20 mg, 0.035 mmol) in MeOH (4.0 mL) at 0 °C was added CSA (8.0 mg, 0.035 mmol). The reaction mixture was warmed to rt over 1 h at which time the reaction was quenched with sat. $NaHCO_3$ (aq., 2.5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 x 5 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 to 3:1 hexanes:ethyl acetate) provided the 16 mg of **2.124** (100%) as a colorless oil. R_f 0.40 (5:1 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = +1.8° (c = 0.22, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.31 (d, *J* = 7.3 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 5.88 (dddd, *J* = 16.6, 10.3, 6.4, 6.4 Hz, 1H), 5.12 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.00 (d, *J* = 10.3 Hz, 1H), 4.34 (s, 2H), 3.44-3.35 (m, 2H), 3.34 (d, *J* = 9.8 Hz, 1H), 3.22-3.13 (m, 2H), 2.47 (dddd, *J* = 14.6, 8.8, 5.9, 5.9 Hz, 1H), 2.24 (dddd, *J* = 16.1, 6.8, 6.8, 6.8 Hz, 1H), 2.02-1.93 (m, 1H), 1.93-1.66 (m, 5H), 1.66-1.45 (m, 5H), 1.12 (s, 3H), 0.95 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.2, 138.9, 128.2, 127.4, 127.3, 114.5, 87.3, 87.1, 77.5, 76.1, 72.6, 70.6, 37.5, 34.6, 30.6, 30.0, 27.8, 27.5, 25.9, 23.7, 18.2, -2.1, -2.1; IR (neat) 3436, 2930, 2856, 1455, 1364, 1253, 1104 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{27}H_{46}O_4SiNa$ 485.3 ($M+Na^+$), found 485.3.



2.122

Preparation of ester 2.122. To a solution of acid **2.123** (9.3 mg, 11.7 μmol) and alcohol **2.124** (9.1 mg, 19.7 μmol) in CH_2Cl_2 (1.5 mL) were added 2-methyl-6-nitrobenzoic anhydride (8.0 mg, 23.3 μmol) and DMAP (7.1 mg, 58.2 μmol). The reaction mixture was stirred at rt overnight before the reaction was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the organic phase was combined, dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) provided **2.122** (12.6 mg, 87%) as a colorless oil. R_f 0.35 (10:1 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = -4.6° (c = 0.32, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.77-7.73 (m, 4H), 7.30 (d, *J* = 7.3 Hz, 2H), 7.24-7.20 (m, 6H), 7.19 (d, *J* = 7.5 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 5.84 (dddd, *J* = 16.8, 10.2, 6.4, 6.4 Hz, 1H), 5.10 (dd, *J* = 17.1, 1.7 Hz, 1H), 5.00 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.91-4.86 (m, 1H), 4.36-4.31 (partially obscured m, 1H), 4.34 (s, 2H), 4.23 (dd, *J* = 11.2, 6.1 Hz, 1H), 4.05 (d, *J* = 11.2, 2.0 Hz, 1H), 4.01 (s, 1H), 3.67 (ddd, *J* = 10.0, 6.3, 6.3 Hz, 1H), 3.61 (ddd, *J* = 10.0, 6.1, 6.1 Hz, 1H), 3.52 (ddd, *J* = 9.3, 6.3, 2.9 Hz, 1H), 3.49-3.45 (m, 1H), 3.43-3.33 (m, 3H), 2.75 (dd, *J* = 12.2, 12.2 Hz, 1H), 2.59 (dd, *J* = 14.9, 8.0 Hz, 1H), 2.49-2.42 (partially obscured m, 1H), 2.42 (partially obscured dd, *J* = 14.9, 6.3 Hz, 1H), 2.24 (dddd, *J* = 15.9, 7.6, 7.6, 7.6 Hz, 1H), 2.00-1.45 (m, 16H), 1.36-1.28 (m, 2H), 1.28 (s, 3H), 1.14 (s, 9H), 1.10 (s, 3H), 1.07 (t, *J* = 7.8 Hz, 9H), 1.00 (d, *J* = 8.3 Hz, 3H), 0.98 (t, *J* = 7.8 Hz, 9H), 0.94 (s, 9H), 0.73 (q, *J* = 7.8 Hz, 3H), 0.72 (q, *J* = 8.1 Hz, 3H), 0.60 (q, *J* = 7.8 Hz, 3H), 0.59 (q, *J* =

8.1 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.0, 139.9, 139.0, 136.4, 134.9, 134.9, 130.2, 128.9, 128.3, 128.0, 127.9, 115.4, 88.2, 84.4, 82.1, 80.9, 78.4, 77.9, 74.5, 73.3, 72.9, 71.2, 71.1, 69.6, 64.7, 45.8, 40.9, 38.1, 35.1, 35.0, 33.5, 30.8, 30.2, 29.8, 28.4, 28.1, 27.5, 26.5, 26.3, 23.6, 19.8, 18.7, 17.1, 12.9, 7.6, 7.6, 5.8, 5.5, -1.5, -1.5; IR (neat) 2954, 2877, 1740, 1464, 1380, 1107 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{71}H_{118}O_{10}Si_4Na$ 1265.8 (M+Na$^+$), found 1265.7.



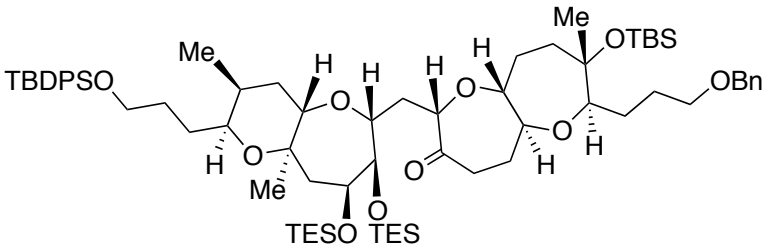
2.127

Preparation of alcohol 2.127. To a solution of $TiCl_4$ (0.226 mL, 2.06 mmol) in CH_2Cl_2 (14 mL) at 0 °C was added THF (1.09 mL, 12.4 mmol) dropwise. To the resulting yellow solution was added TMEDA (1.87 mL, 12.4 mmol) dropwise. The ice bath was removed and the mixture was allowed to stir for 15 min. Activated Zn dust (301 mg, 4.66 mmol) and $PbCl_2$ (68.0 mg, 0.245 mmol) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3-5 min. To the slurry was transferred a solution of ester **2.122** (20.0 mg, 16.1 μmol) and CH_3CHBr_2 (0.185 mL, 2.06 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was then heated to reflux for 2 hr before it was cooled to 0 °C and quenched with sat. K_2CO_3 (aq., 1.0 mL). After stirring for 30 min at 0 °C, the resulting mixture was filtered. The filtrate was concentrated and flash chromatography (3:1 hexanes:ethyl acetate) gave a mixture of cyclic enol ether **2.121** and acyclic enol ether **2.125**.

To a solution of the mixture obtained from above in benzene (5 mL) was added Grubbs' 2nd generation catalyst **2.62** (3 mg, 3.53 μmol). The reaction mixture was heated to reflux under 1 atm. of ethylene for 16 h. A second portion of Grubbs' 2nd generation catalyst **2.62** (3 mg, 3.53 μmol) was added and the ethylene balloon was removed. The reaction mixture was heated for another 16 h before it was cooled to rt. The solvent was removed in vacuo and the residue was quickly passed through a plug of silica (hexanes: ethyl acetate 20:1). The resulting 6:1 mixture of oxepene and dihydropyran was used in the next step without further purification.

To a solution of enol ethers from above in CH_2Cl_2 (5 mL) at -78 °C was added a solution of dimethyl dioxirane (0.31 mL of 0.10 M solution in CH_2Cl_2, 0.031 mmol) dropwise. The reaction mixture was warmed to 0 °C and then concentrated. The resulting residue was dissolved in CH_2Cl_2 (5 mL) and the reaction mixture was cooled to -78 °C, at which temperature, a solution of *i*Bu_2AlH (50.0 μL of 1.0 M solution in THF, 50.0 μmol) was added. The reaction mixture was stirred for 2 h and the reaction was quenched with sat. NH_4Cl (aq., 3 mL) and allowed to warm to rt. Saturated potassium sodium tartrate solution (10 mL) was added and the mixture was stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the organic phase was combined, dried (Na_2SO_4) and concentrated. Flash chromatography (7:1 hexanes:ethyl acetate) gave alcohol **2.127** (9.6 mg, 49% 3 steps). R_f 0.35 (4:1 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = -3.3° (c = 0.58, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.80-7.75 (m, 4H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.26-7.19 (m, 8H), 7.12 (t, *J* = 7.3 Hz, 1H), 4.37 (s, 2H), 4.30 (dd, *J* = 9.0, 8.3 Hz, 1H), 4.18 (dd, *J* = 8.0, 4.9 Hz, 1H), 4.10 (dd, *J* = 12.0, 2.2 Hz, 1H), 4.07 (s, 1H), 3.81 (ddd, *J* = 6.1, 6.1, 2.7 Hz, 1H), 3.68 (ddd, *J* = 10.0, 6.6, 6.6 Hz, 1H), 3.66-3.60 (m, 2H),

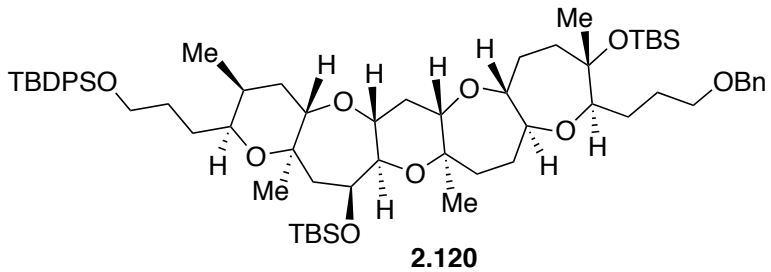
3.50-3.36 (m, 6H), 2.78 (dd, *J* = 12.1, 12.1 Hz, 1H), 2.15-1.92 (m, 3H), 1.91-1.40 (m, 18H), 1.40-1.25 (m, 2H), 1.28 (s, 3H), 1.16 (s, 9H), 1.13 (t, *J* = 8.1 Hz, 9H), 1.11 (s, 3H), 1.01 (t, *J* = 8.1 Hz, 9H), 0.96 (d, *J* = 7.3 Hz, 3H), 0.95 (s, 9H), 0.77 (q, *J* = 7.8 Hz, 3H), 0.76 (q, *J* = 8.0 Hz, 3H), 0.64 (q, *J* = 7.8 Hz, 3H), 0.63 (q, *J* = 8.0 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.6, 136.1, 134.6, 134.5, 129.9, 128.5, 128.4, 128.1, 127.7, 127.5, 88.8, 87.6, 86.0, 83.4, 83.1, 80.7, 77.9, 74.1, 73.5, 73.0, 72.4, 70.9, 70.8, 69.5, 64.3, 45.4, 40.6, 38.6, 34.7, 33.2, 30.2, 29.8, 29.7, 29.6, 29.5, 29.1, 27.9, 27.8, 27.2, 26.1, 24.3, 19.5, 18.4, 16.8, 12.4, 7.4, 7.2, 5.6, 5.2, -1.9, -2.1; IR (neat) 3463, 2932, 2876, 1458, 1380, 1251, 1083, 1005 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{70}H_{118}O_{10}Si_4Na$ 1253.8 (M+Na$^+$), found 1253.8.



2.128

Preparation of ketone 2.128. To a solution of alcohol **2.128** (8.7 mg, 7.07 μmol) in CH_2Cl_2 (5 mL) were added activated 4Å MS (12 mg), NMO (12.2 mg, 0.104 mmol) and TPAP (1 mg, 0.003 mmol). The reaction mixture was stirred at rt for 2 h before the solvent was removed in vacuo. Flash chromatography (10:1 hexanes:ethyl acetate) gave 7.6 mg of ketone **2.128** (87%) as a colorless oil. R_f 0.65 (5:1 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = -14.2° (c = 1.0, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.80-7.76 (m, 4H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.26-7.19 (m, 8H), 7.14 (t, *J* = 7.3 Hz, 1H), 4.37 (s, 2H), 4.29 (dd, *J* = 11.5, 5.9 Hz, 1H), 4.19 (dd, *J* = 9.5, 4.4 Hz, 1H), 4.09 (dd, *J* = 11.2, 2.2 Hz, 1H), 4.02 (s, 1H), 3.91 (dd, *J* = 5.4, 5.4 Hz, 1H), 3.71 (ddd, *J* = 10.0, 6.4, 6.4 Hz, 1H), 3.65

(ddd, *J* = 10.0, 6.4, 6.4 Hz, 1H), 3.50-3.36 (m, 5H), 2.87 (dd, *J* = 12.5, 12.5 Hz, 1H), 2.80-2.73 (m, 2H), 2.31 (dd, *J* = 11.5, 6.6 Hz, 1H), 2.24 (ddd, *J* = 14.4, 9.8, 5.1 Hz, 1H), 2.14-2.04 (m, 2H), 1.95-1.85 (m, 2H), 1.83-1.65 (m, 8H), 1.63-1.42 (m, 6H), 1.38-1.32 (m, 1H), 1.31 (s, 3H), 1.18 (s, 9H), 1.10 (t, *J* = 7.8 Hz, 9H), 1.08 (s, 3H), 1.03 (t, *J* = 7.8 Hz, 9H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.95 (s, 9H), 0.74 (q, *J* = 7.6 Hz, 3H), 0.73 (q, *J* = 8.1 Hz, 3H), 0.66 (q, *J* = 7.8 Hz, 3H), 0.65 (q, *J* = 8.1 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 214.3, 139.8, 136.4, 134.9, 130.2, 129.1, 128.9, 128.7, 128.1, 128.0, 88.7, 88.6, 87.5, 85.0, 82.8, 79.5, 78.0, 74.6, 73.4, 72.6, 71.2, 71.0, 69.6, 64.7, 45.8, 39.4, 38.7, 38.1, 35.0, 33.5, 32.0, 30.4, 30.2, 29.8, 29.6, 28.2, 28.1, 27.5, 26.4, 24.9, 19.8, 18.7, 17.1, 12.8, 7.6, 7.6, 5.8, 5.5, -1.7, -1.8; IR (neat) 2952, 2876, 1720, 1459, 1430, 1380, 1251, 1106, 1005, 831, 740, 703 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{70}H_{116}O_{10}Si_4Na$ 1251.8 ($M+Na^+$), found 1251.7.



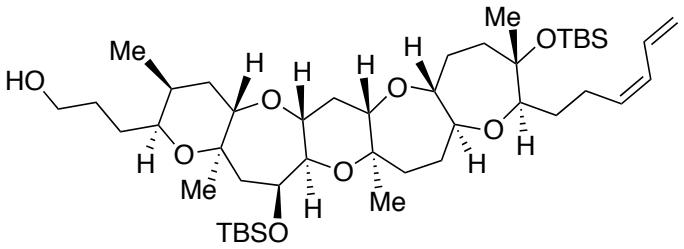
2.120

Preparation of brevenal pentacyclic core 2.120. To a solution of **2.128** (5.9 mg, 4.80 μmol) in CH_2Cl_2 (1.5 mL) and EtSH (0.5 mL) was added $Zn(OTf)_2$ (10 mg, 27.5 μmol). The reaction mixture was stirred at rt overnight before it was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes:ethyl acetate) provided 2.9 mg of *O,S*-mixed ketal **2.129** as a colorless oil (58%).

To the solution of **2.129** in CH_2Cl_2 (3 mL) were added 2,6-lutidine (30 μL, 0.26 mmol) and TBSOTf (30 μL, 0.13 mmol). The reaction mixture was stirred for 6 h before the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (15:1 hexanes:ethyl acetate) provided 2.6 mg of the TBS ether as a colorless oil (82%).

To the solution of the TBS ether from above in CH_2Cl_2 (2 mL) at 0 °C was added $ZnMe_2$ (95.0 μL of a 1.0 M solution in heptane, 95.0 μmol) and $Zn(OTf)_2$ (10.4 mg, 28.6 μmol). The cold bath was removed and the reaction mixture was warmed to rt and stirred overnight. The solvent was removed in vacuo and flash chromatography (15:1 hexanes:ethyl acetate) provided 2.3 mg of **2.120** as a colorless oil (94%). R_f 0.50 (15:2 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = -17.9° (c = 0.437, benzene); ^{1}H NMR (500 MHz, C_6D_6) δ 7.82-7.78 (m, 4H), 7.34 (d, *J* = 7.7 Hz, 2H), 7.26-7.22 (m, 6H), 7.20 (d, *J* = 7.7 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 4.42 (dd, *J* = 12.1, 5.5 Hz, 1H), 4.38 (s, 2H), 4.04 (dd, *J* = 3.9, 3.9 Hz, 1H), 3.93 (ddd, *J* = 11.7, 9.1, 4.3 Hz, 1H), 3.68 (ddd, *J* = 9.9, 6.2, 6.2 Hz, 1H), 3.65 (ddd, *J* = 9.9, 6.2, 6.2 Hz, 1H), 3.56-3.38 (m, 4H), 3.37-3.31 (m, 2H), 3.24 (ddd, *J* = 9.0, 9.0, 4.4 Hz, 1H), 3.18 (dd, *J* = 12.1, 4.1 Hz, 1H), 2.35 (ddd, *J* = 12.1, 4.4, 4.4 Hz, 1H), 2.26-2.17 (m, 2H), 2.14-1.71 (m, 13H), 1.67-1.44 (m, 5H), 1.40-1.24 (m, 2H), 1.25 (s, 3H), 1.19 (s, 9H), 1.15 (s, 3H), 1.13 (s, 3H), 1.10 (s, 9H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.9, 136.4, 134.9, 130.2, 129.2, 129.0, 128.9, 128.4, 128.0, 127.9, 126.7, 89.0, 86.9, 85.2, 83.4, 78.4, 78.0, 76.9, 76.5, 74.0, 73.7, 73.6, 73.4, 71.5, 71.2, 64.7, 50.3, 38.4, 38.4, 35.9, 35.0, 33.6, 30.5, 30.2, 29.9, 29.8, 28.1, 27.5, 26.6, 26.4, 24.4,

21.6, 19.8, 18.9, 18.7, 16.3, 13.2, -1.6, -1.7, -3.6, -4.4; IR (neat) 2930, 2856, 1460, 1381, 1252, 1085 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{65}H_{104}O_9Si_3Na$ 1135.7 ($M+Na^+$), found 1135.7.



2.133

Preparation of primary alcohol 2.133. To a solution of **2.120** (6.0 mg, 5.40 μmol) in THF (3 mL) at -78 °C was added excess LiDBB (ca. 0.17 M solution in THF (see below for experimental protocol) until the blue color of LiDBB persisted. After 1 h, the reaction was quenched with sat. NH_4Cl (aq., 5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes:ethyl acetate) provided the corresponding primary alcohol as a colorless oil (5.2 mg, 95%).

0.17 M LiDBB solution in THF: To a mixture of di-*tert*-butylbiphenyl (0.37 g, 1.4 mmol) in THF (8 mL) at 0 °C was added lithium metal (60 mg, 8.6 mmol). The resulting mixture was sonicated at 0 °C for 1 h and then stirred at 0 °C for 1 h.

To a solution of the primary alcohol obatined from above (5.2 mg, 5.1 μmol) and DMSO (0.2 mL) in CH_2Cl_2 (0.8 mL) at 0 ^oC were added Et_3N (65 μL, 0.467 mmol) and SO_3•Py (37.3 mg, 0.235 mmol). The reaction mixture was stirred at rt for 1 h before the reaction was quenched with sat. NH_4Cl (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phase was dried (Na_2SO_4) and

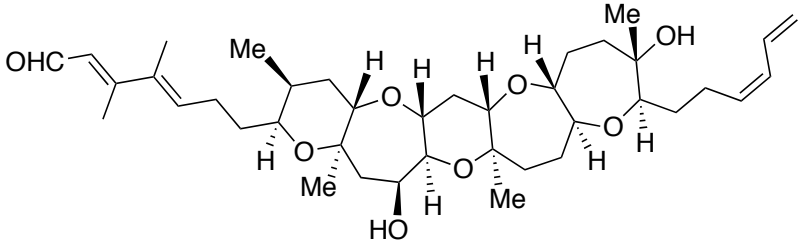
concentrated. The resulting residue was passed through a plug of silica gel. Aldehyde **2.130** was used immediately in the next step.

To a suspension of phosphonium salt **2.131** (126.7 mg, 0.235 mmol) in THF (0.3 mL) at -30 °C was added NaHMDS (0.19 mL of 1.0 M solution in THF, 0.19 mmol). After stirring for 15 min, the resulting mixture was cooled to -78 °C. To this solution was added a pre-cooled (-78 °C) solution of aldehyde **2.130** (5.1 μmol) in THF (1.0 mL). The resulting reaction mixture was allowed to slowly warmed up to rt and stirred at rt for 15 min before the reaction was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was passed through a silica gel plug and used in the next step without further purification.

To the solution of the phenylselenide obtained from above in THF (0.6 mL) was added $NaHCO_3$ (7.9 mg, 0.094 mmol) and H_2O_2 (0.2 mL of 30% aq. solution). The reaction mixture was warmed to 30 °C and stirred for 21 h after which the reaction was quenched with sat. Na_2SO_3 (aq., 5 mL) at 0 °C. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (20:1 hexanes:ethyl acetate) provided 4.6 mg of diene **2.132** as a colorless oil (87% 3 steps).

To a solution of **2.132** (6.0 mg, 5.7 μmol) in THF (0.3 mL) was added a solution of TBAF/AcOH (0.1 mL, prepared from 0.5 mL of TBAF (1.0 M solution in THF) and 30 μL AcOH). After 9 h, the reaction was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate)

provided 4.2 mg of primary alcohol **2.133** as a colorless oil (91%). R_f 0.50 (1:1 hexanes:ethyl acetate) $[\alpha]_D^{20}$ = -18.0° (c = 0.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.67 (ddd, *J* = 16.6, 10.2, 10.2 Hz, 1H), 6.05 (dd, *J* = 11.2, 11.2 Hz, 1H), 5.46 (dd, *J* = 18.1, 8.3 Hz, 1H), 5.21 (d, *J* = 17.1 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 4.26 (dd, *J* = 11.7, 4.9 Hz, 1H), 4.01 (br s, 1H), 3.75 (ddd, *J* = 14.2, 12.2, 4.9 Hz, 1H), 3.68 (ddd, *J* = 11.2, 6.4, 4.9 Hz, 1H), 3.60 (ddd, *J* = 10.8, 7.3, 5.4 Hz, 1H), 3.56-3.52 (m, 1H), 3.34-3.21 (m, 4H), 3.15 (dd, *J* = 12.2, 3.9 Hz, 1H), 2.36-2.28 (m, 2H), 2.20-1.50 (m, 18H), 1.50-1.37 (m, 3H), 1.27 (s, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.95 (s, 9H), 0.87 (s, 9H), 0.10 (s, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.7, 132.1, 129.6, 117.1, 86.9, 86.2, 85.2, 82.0, 78.4, 77.2, 76.1, 75.5, 73.2, 72.4, 72.3, 62.8, 49.2, 37.7, 37.6, 34.8, 33.8, 33.4, 30.5, 30.4, 30.0, 29.7, 28.7, 25.9, 25.7, 24.7, 23.9, 20.5, 18.1, 18.0, 16.2, 12.5, -2.0, -2.2, -4.3, -5.0; IR (neat) 3421, 2929, 2854, 1733, 1464, 1377, 1253, 1216, 1083 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{45}H_{82}O_8Si_2Na$ 829.6 ($M+Na^+$), found 829.6.



brevenal (**2.4**)

Preparation of brevenal 2.4. To the solution of the primary alcohol **2.133** (4.2 mg, 5.2 μmol) in CH_2Cl_2 (0.6 mL) and DMSO (0.2 mL) at 0 °C were added Et_3N (62 μL, 0.447 mmol) and SO_3•Py (35.4 mg, 0.224 mmol). The resulting mixture was stirred at rt for 1 h before the reaction was quenched with sat. NH_4Cl (aq., 5 mL). The aqueous

phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. The resulting residue that contained aldehyde **2.134** was passed through a sílica gel plug and used for the next step without further purification.

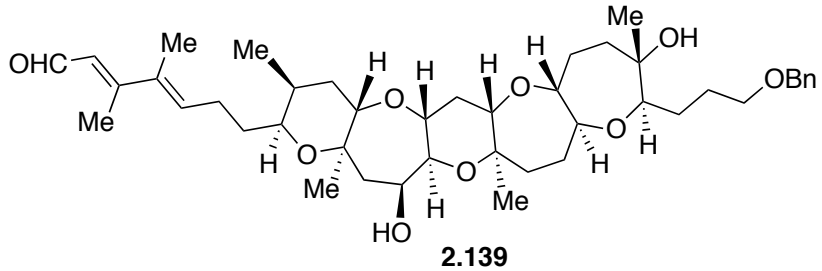
To the solution of the phosphonate **2.135** (92.3 mg, 0.349 mmol) in THF (0.3 mL) at -78 °C was added *n*BuLi (0.11 mL of a 2.5 M solution in THF, 0.28 mmol). After stirring for 10 min at -78 °C, the mixture was warmed to 0 °C and stirred for an additional 50 min. The reaction mixture was then cooled back to -78 °C and added a precooled (-78 °C) solution of the aldehyde **2.134** (5.2 μmol) obtained from above in THF (1.0 mL). The resulitng mixture was slowly warmed to rt and stirred for 26 h before it was quenched with sat. NH_4Cl (aq., 5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. Flash chromatography (30:1 hexanes:ethyl acetate) provided 4.0 mg of **2.136** as a colorless oil (85%, 2 steps).

To a solution of **2.136** (2.4 mg, 2.6 μmol) in THF (0.2 mL) at 0 °C was added HF•Py (0.1 mL, 6 mmol). After 3 h, the reaction mixture was poured into a precooled (0 °C) solution of sat. $NaHCO_3$ (aq., 30 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was passed through a plug of silica gel to give a diol that was used in the next step without further purification.

To a solution of the diol from above in CH_2Cl_2 (0.5 mL) at -78 °C was added *i*Bu_2AlH (10 μL of 1.0 M solution in hexanes, 10.0 μmol). The reaction mixture was stirred at -78 °C for 15 min before the reaction was quenched with sat. NH_4Cl (aq., 5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined

extracts were dried (Na_2SO_4) and concentrated. The resulting residue which contained the corresponding triol was used directly in the subsequent oxidation reaction.

To a solution of triol from above in CH_2Cl_2 (0.5 mL) at rt was added MnO_2 (4.0 mg, 46 μmol). After stirring for 10 min, the mixture was directly loaded onto a silica gel column. Flash chromatography (2:1 hexanes:ethyl acetate) provided brevenal **2.4** as a colorless oil (1.4 mg, 80% 3 steps). R_f 0.45 (1:1 hexanes:ethyl acetate); $[\alpha]_D^{20}$ = -28.6° (c = 0.07, benzene); ^{1}H NMR (500 MHz, C_6D_6) δ 10.09 (d, *J* = 6.8 Hz, 1H), 6.78 (ddd, *J* = 16.6, 11.0, 11.0 Hz, 1H), 6.15 (d, *J* = 7.5 Hz, 1H), 6.09 (dd, *J* = 10.6, 10.6 Hz, 1H), 5.82 (dd, *J* = 7.0, 7.0 Hz, 1H), 5.46 (ddd, *J* = 10.5, 8.6, 8.6 Hz, 1H), 5.17 (d, *J* = 16.6 Hz, 1H), 5.06 (d, *J* = 10.0 Hz, 1H), 4.08 (br s, 1H), 4.01 (dd, *J* = 10.7, 6.1 Hz, 1H), 3.71 (ddd, *J* = 11.5, 11.5, 5.4 Hz, 1H), 3.46 (dd, *J* = 9.7, 2.0 Hz, 1H), 3.35 (ddd, *J* = 7.3, 7.3, 7.3 Hz, 1H), 3.29 (d, *J* = 9.3 Hz, 1H), 3.21-3.16 (m, 2H), 2.95 (dd, *J* = 12.2, 3.2 Hz, 1H), 2.38-2.30 (m, 4H), 2.30-2.20 (m, 1H), 2.19-2.09 (m, 3H), 2.07-1.96 (m, 1H), 1.96-1.82 (m, 2H), 1.80 (s, 3H), 1.80-1.71 (m, 4H), 1.71-1.56 (m, 4H), 1.56 (s, 3H), 1.56-1.40 (m, 4H), 1.19 (s, 3H), 1.14 (s, 3H), 1.13-1.07 (m, 1H), 0.98 (s, 3H), 0.97 (d, *J* = 9.7 Hz, 3H), 0.55 (br s, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 190.7, 156.3, 135.9, 134.6, 133.0, 132.7, 130.2, 126.1, 117.3, 87.4, 86.2, 84.8, 82.0, 77.3, 76.8, 76.5, 75.1, 74.1, 73.7, 70.9, 70.0, 47.9, 38.6, 37.7, 35.4, 34.6, 33.5, 32.7, 30.7, 29.9, 29.4, 26.5, 25.2, 23.6, 19.4, 16.2, 14.0, 13.8, 12.9; IR (neat) 3463, 2985, 1742, 1661, 1618, 1448, 1374, 1242, 1093, 1048 cm^{-1}; ESI-TOF/HRMS (*m/z*) calcd for $C_{39}H_{60}O_8Na$ 679.4186 ($M+Na^+$), found 679.4200.



2.139

Preparation of brevenal analogue 2.139. **2.139** was prepared from **2.120** according to the same procedures that were used to convert **2.132** to **2.4** (51% 6 steps). R_f 0.40 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -25.0° (c = 0.10, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 10.10 (d, *J* = 7.6 Hz, 1H), 7.35-7.30 (m, 2H), 7.20-7.15 (m, 2H), 7.10 (t, *J* = 7.1 Hz, 1H), 6.14 (d, *J* = 7.0 Hz, 1H), 5.82 (dd, *J* = 7.0, 7.0 Hz, 1H), 5.52 (br s, 1H), 5.12 (br s, 1H), 4.40 (d, *J* = 12.4 Hz, 1H), 4.35 (d, *J* = 12.2 Hz, 1H), 4.06 (br s, 1H), 4.00 (dd, *J* = 11.0, 5.9 Hz, 1H), 3.70 (ddd, *J* = 11.0, 9.7, 4.4 Hz, 1H), 3.47-3.34 (m, 4H), 3.29 (d, *J* = 9.0 Hz, 1H), 3.21-3.16 (m, 2H), 2.93 (dd, *J* = 12.2, 3.9 Hz, 1H), 2.36-2.30 (m, 2H), 2.30-2.20 (m, 2H), 2.18-1.80 (m, 6H), 1.80 (s, 3H), 1.79-1.60 (m, 7H), 1.60-1.56 (m, 2H), 1.56 (s, 3H), 1.56-1.20 (m, 4H), 1.18 (s, 3H), 1.11 (s, 3H), 1.01 (s, 3H), 0.96 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 190.7, 156.3, 139.5, 135.9, 134.6, 126.1, 115.0, 88.6, 86.3, 84.8, 82.1, 77.3, 76.8, 76.5, 75.1, 74.2, 73.8, 73.2, 70.9, 69.9, 47.9, 38.6, 37.7, 35.4, 34.6, 33.5, 32.7, 30.1, 29.8, 29.5, 27.9, 27.8, 26.5, 23.6, 19.4, 16.1, 14.0, 13.8, 12.9; IR (neat) 3456, 3058, 2986, 1736, 1659, 1446, 1374, 1246, 1095, 1047 cm^{-1}; ESI-TOF/HRMS (*m/z*) calcd for $C_{43}H_{64}O_9Na$ 747.5 ($M+Na^+$), found 747.4.

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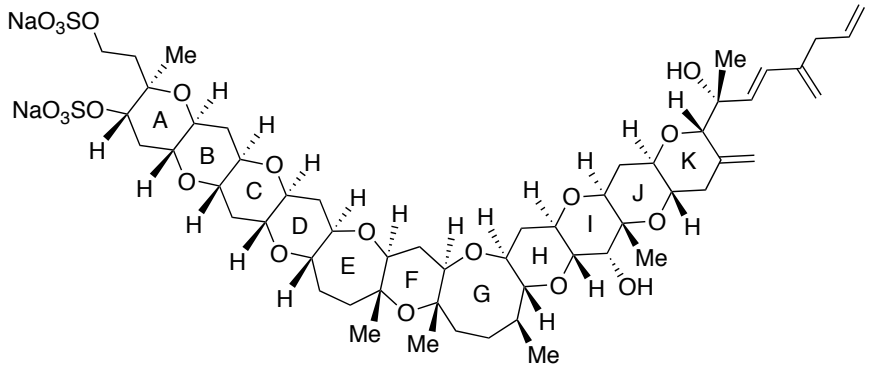
CHAPTER 3

EFFORTS TOWARDS THE SYNTHESIS OF YESSOTOXIN AND ADRIATOXIN

Introduction

Yessotoxins (YTXs) are a class of structurally related compounds that belong to the marine polycyclic ether natural product family.[1,2] The parent compound of this class, yessotoxin (YTX, **3.1**, Figure 3.1) was first isolated in 1987 by Yasumoto and co-workers from the digestive gland of the scallop *Patinopecten yessoensis* collected in Mutsu Bay, Japan.[3] Later it was found that YTX is actually produced by phytoplanktonic dinoflagellates *Protoceratium reticulatum*, *Lingulodinium polyedrum*, and *Gonyaulax spinifera* and accumulated in filter feeding shellfish exposed to these dinoflagellates.[4] The



yessotoxin (YTX, **3.1**)

Figure 3.1. Structure of yessotoxin (YTX, **3.1**)

relative stereochemistry of YTX was determined using extensive nOe studies,[5] and the absolute configuration was subsequently assigned using a chiral anisotropic reagent in NMR studies.[6] To date, there are about 100 YTX analogues that have been reported from both shellfish and dinoflagellates, however, only about 40 of them have been identified and characterized.[2b] It has been suggested that some YTXs are directly synthesized by dinoflagellates while others are shellfish metabolism products.[7]

YTXs were originally classified as diarrhetic shellfish poisoning (DSP) toxins because they are often concomitantly extracted with other DSP toxins such as okadaic acid (OA) and dinophysistoxins (DTXs), and give positive results when tested in conventional bioassays for DSP toxins.[8] However, recent evidence has suggested that YTXs should be excluded from the DSP toxins because they do not cause diarrhea or inhibit protein phosphatases as OA and DTXs.[9] Although about 40 YTXs have been already identified and characterized, only very few of them have undergone thorough toxicological studies. As a result, the toxicological potential of YTXs is still not fully understood.

YTX (**3.1**) is highly toxic by intraperitoneal injection (i.p.) to mice with LD_{50} ranging from 80-750 μg/Kg depending on experimental conditions.[9,10] The symptoms exhibited by mice injected with lethal dose of YTX include dyspnea, restlessness, shivering, and cramps, which are similar to those caused by paralytic shellfish poisoning (PSP) toxins. The target organ of YTX appears to be the cardiac muscle, where it induces ultrastructural changes.[9,10b] It has also been reported that YTX produces neuronal damage in the brain and causes inflammatory response in the duodenum and thymus of mice.[11] However, contrary to the high toxicity observed in the i.p. experiments, YTX is not lethal

to mice after either acute oral administration at doses up to 54 mg/kg or repeated oral administration at 2 mg/kg/day for 7 days.[12] Neither diarrhea nor damages of main organs have been observed. The vast difference between the i.p. and oral toxicity suggests that even though YTX is potentially toxic for humans, it is poorly absorbed in the gastrointestinal tract.

In vitro studies have shown that YTX can induce apoptotic cell death in different types of cells, such as human Hela cells, human neuroblastoma cells, and rodent myoblast cells by activating different caspase isoforms.[13] Even though several possible modes of action of YTX have been proposed, a precise mechanism of action is still missing. It has been suggested that YTX acts as a mitochondrial permeability transition pore (PTP) opener and causes mitochondrial membrane depolarization, thus leading to cell apoptosis.[14] In addition, there is evidence suggesting that lysosomes are one of the cellular components that are involved in YTX-induced cell death as well.[15]

Interestingly, unlike other marine polycyclic ether natural products such as the brevetoxins and ciguatoxins, which exert potent neurotoxicity by binding to site 5 of voltage gated sodium channels (VGSC) on excitable membranes, VGSC appear not to be involved in YTX-induced cell death.[16] However, it seems YTX can exert a modest, and probably indirect effect on voltage-sensitive calcium channels and modulate the calcium homeostasis in both human lymphocytes and rat cerebellar neurons.[16b,17] It has also been shown that calcium movements induced by YTX was not the cause of YTX-induced cell death, since in the presence of calcium channel blockers apoptosis still occurred.[16b]

In another assay conducted by Rossini and co-workers, YTX was shown to be able to disrupt the degradation pathway of E-cadherins in epithelial cells at low

nanomolar concentrations.[18] E-cadherins are calcium-dependent transmembrane proteins that are involved in cell-cell and cell-substrate adhensions. Altered E-cadherins expression has been associated with tumor spreading and metastasis formation in human cancers.[19] Thus YTX-induced disruption of E-cadherin degradation has raised some concern that YTX may cause the loss of the tumor-suppressing function of E-cadherins.[12d] It was suggested by Rossini and co-workers that YTX affects the degradation pathway of E-cadherin by inhibiting the internalization and complete degradation of E-cadherin fragments, either through direct interaction or alteration of effectors located on the plasma membrane.[18b] The author also proposed that YTX-induced cell death might be a secondary consequence stemming from the alteration of endocytosis and turnover of some plasma membrane proteins other than E-cadherins.[18c]

Despite the recent progress in the toxicological studies, the full toxicological potential of YTXs remains to be fully elucidated. For instance, in vivo toxicity studies in animals other than mice, as well as pharmacokinetic studies regarding absorption and accumulation of YTXs are still lacking. The inadequate supply of YTXs remains a constraint for further biological testing despite the identification of their source organisms. Thus, a number of research groups including ours have become interested in pursuing the chemical synthesis of YTXs.

Structurally, YTX contains an array of 11 *trans*-fused ether rings with a triene side chain and two sulfate ester groups. The undecacyclic core of YTX is decorated with five methyl groups, four of them being angular, and consists of a very challenging 7-6-8 EFG ring substructure. Thus, from a synthetic point of view, YTX is a highly intriguing target.

Although there have been no total syntheses of YTX or its analogue so far, syntheses of fragments of YTX have been reported.[20,21,22,23]

During our synthetic program towards the total syntheses of YTX and its analogues, one specific analogue named adriatoxin (ATX, **3.2**, Figure 3.2) emerged above the others. ATX was first isolated in 1998 by Fattorusso and co-workers from the digestive glands of DSP-infested mussel *Mytilus galloprovincialis* collected in the Adriatic Sea.[24] Structurally, the polycyclic backbone of ATX is identical to that of the A-J ring system of YTX, only lacking the K-ring and the triene side chain. The biological activity of ATX is fundamentally unknown, except that the original isolation paper mentioned that ATX is slightly less toxic than YTX in a mouse assay. The very limited availability of ATX from the natural source has hindered the authors from further biological studies. It is for this reason, and because ATX represents a truncated and simplified analogue of YTX, that we decided to choose it as an initial synthetic target in our early stage studies to test our synthetic strategies. Due to the high structural similarities between ATX and YTX, we believe the information gathered from the ATX synthetic study should be applicable to the synthesis of YTX as well.

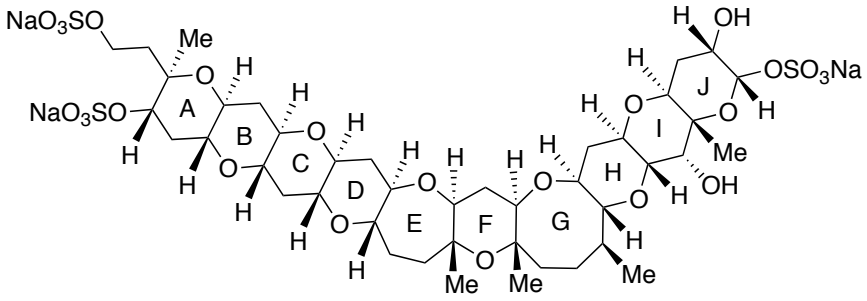


Figure 3.2. Structure of adriatoxin (ATX, **3.2**)

Previous Synthetic Studies Towards Yessotoxin and Adriatoxin

No total synthesis of ATX has been reported to date. However, various fragments of ATX have already been synthesized. There are four other research groups that are active in the synthetic studies on YTX/ATX besides ours, namely the Nakata group,[20] the Mori group,[21] the Kadota group,[22] and the Oishi group.[23] The following is a brief summary of the previous synthetic efforts towards YTX/ATX from these research laboratories.

Nakata's Synthesis of the A-F Ring System of YTX/ATX

In 2002, Nakata and co-workers reported their synthesis of the A-F ring system of YTX/ATX utilizing a convergent coupling strategy. The two coupling partners, alkyne **3.4** and triflate **3.6**, can be synthesized from 2-deoxy-L-ribose (**3.3**) and 2-deoxy-D-ribose (**3.5**) respectively (Figure 3.3). Nakata and co-workers employed a SmI_2-induced radical cyclization and 6-*endo* epoxide opening reaction to construct the D-F ring coupling precursor **3.6**.[20] Treatment of primary triflate **3.6** with the lithium acetylide generated from terminal alkyne **3.4** resulted in the formation of an internal alkyne, which after removal the acetonide protecting group and reprotection with TBS groups afforded alkyne **3.7**. The alkyne was subsequently oxidized using RuO_2 and $NaIO_4$ to give diketone **3.8**. When **3.8** was subjected to CSA and $CH(OMe)_3$ in refluxing methanol, diketal **3.9** was formed, which was successfully reduced using Et_3SiH and TMSOTf to give the A-F ring system of YTX/ATX **3.10**.

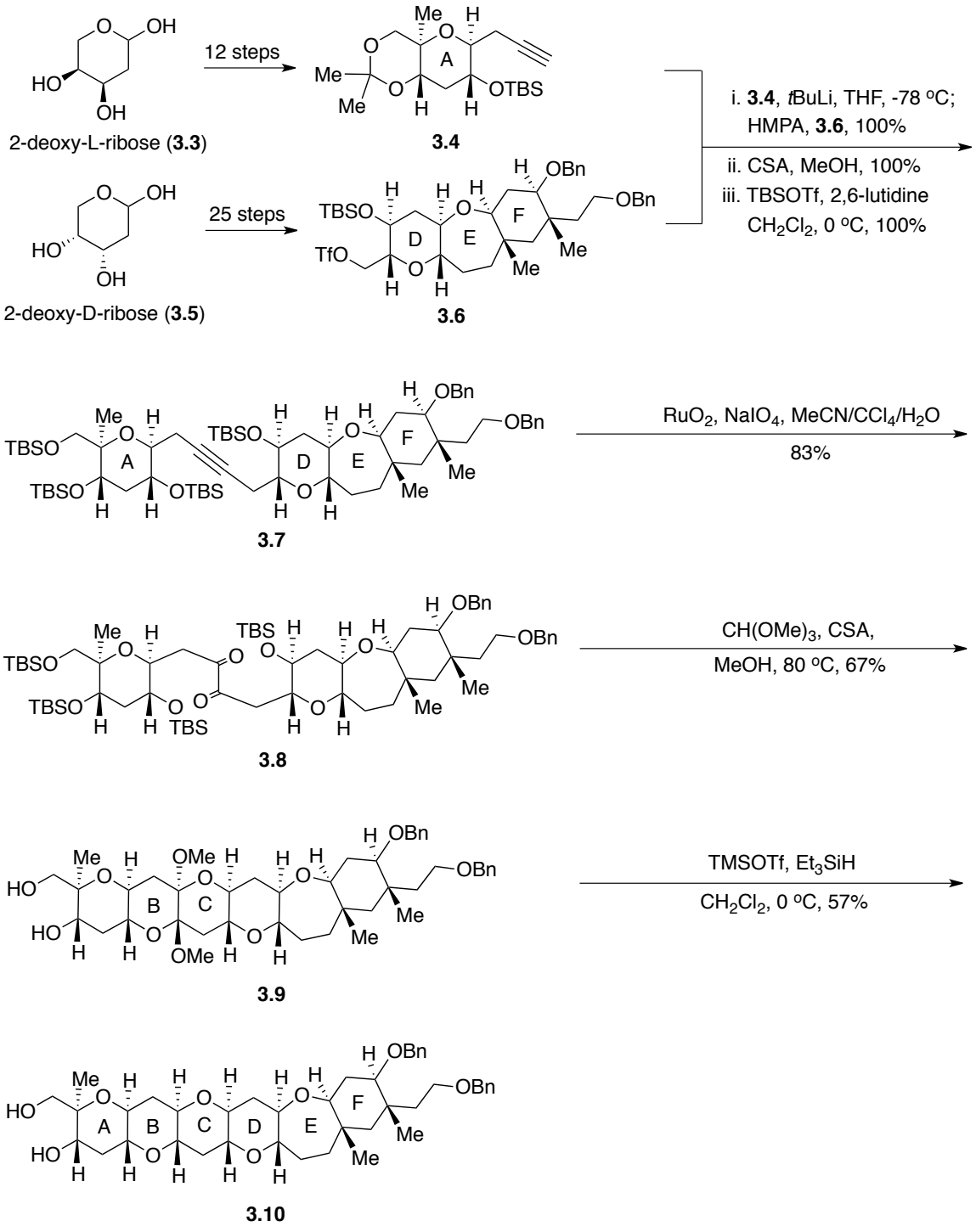


Figure 3.3. Nakata's synthesis of the A-F ring system of ATX

Mori's Synthesis of the A-F Ring System of YTX/ATX

Mori and co-workers have achieved the synthesis of the A-F ring system of YTX/ATX using two different strategies; one iterative[21b] and one convergent.[21c] Mori and co-workers began their iterative synthesis from D-glucose (**3.11**), which was converted into triflate **3.12** in twelve steps (Figure 3.4). Treatment of **3.12** with the sulfonyl-stabilized oxiranyl anion generated from **3.13** led to the formation of epoxide **3.14**.[25] When **3.14** was exposed to acid, desilylation and subsequent stereospecific 6-*endo* cyclization proceeded smoothly to give the B ring of YTX/ATX as ketone **3.15**, which was then converted into another triflate **3.16** in three steps. The five-step reaction sequence was applied three times consecutively to generate pentacyclic ketone **3.17**. The seven-membered E ring of YTX/ATX was formed through a ring-expansion reaction from **3.17** using $TMSCHN_2$ and $BF_3{\bullet}OEt_2$. Primary triflate **3.19** was obtained in another five steps from **3.17**, and was subjected to the oxiranyl anion coupling reaction again. Subsequent acid-promoted cyclization gave ketone **3.21**, which was converted into the A-F ring system of YTX/ATX **3.22** in two steps. Although this iterative strategy was conceptually very simple and efficient, Mori and co-workers felt that the length of this synthesis had comprised its efficiency. They later adopted a revised and more convergent approach that was very similar to Nakata's to construct the A-F ring system of YTX/ATX while still employed their oxiranyl anion coupling chemistry to synthesize the coupling partners.[21c]

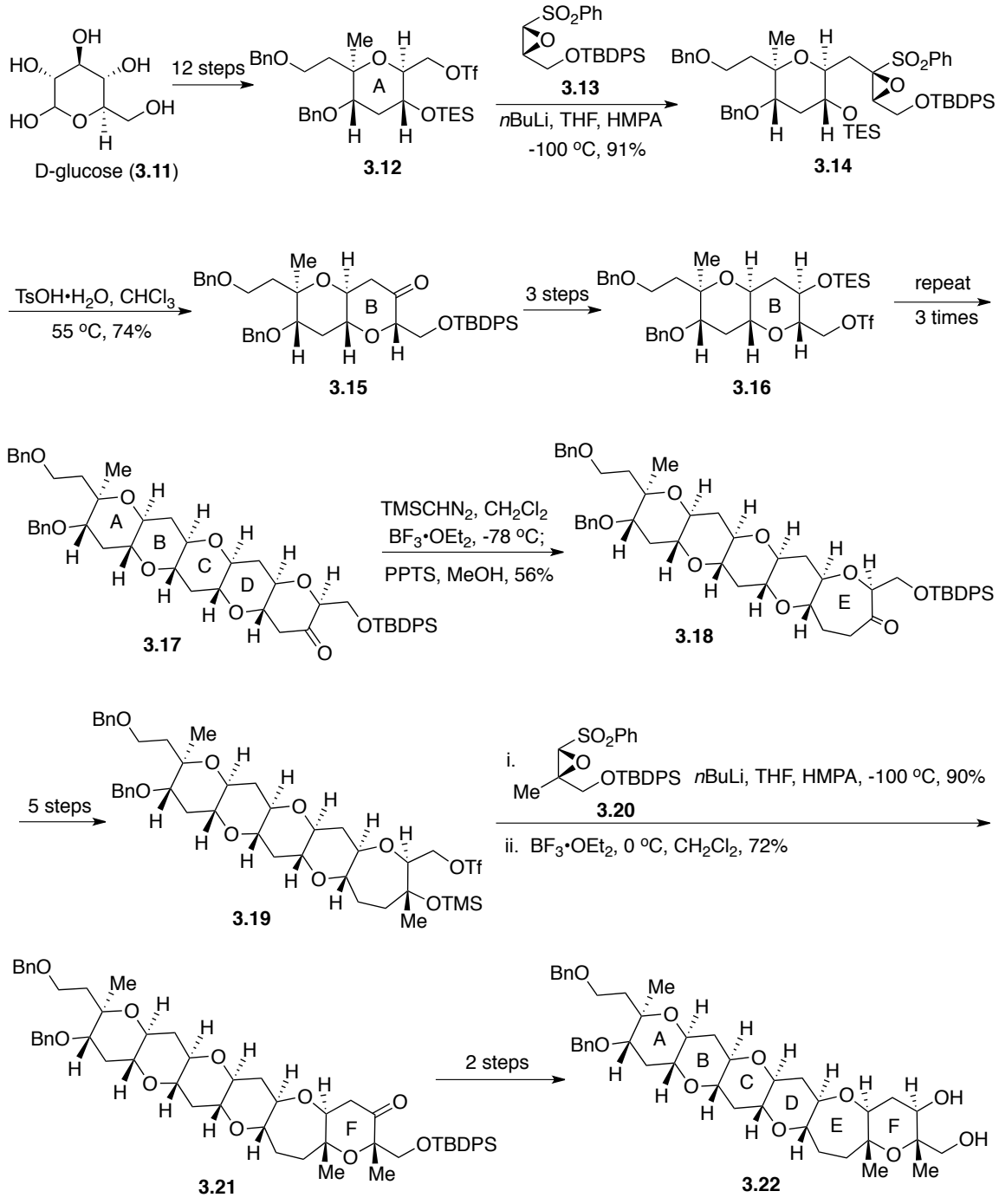


Figure 3.4. Mori's synthesis of the A-F ring system of ATX

Kadota's Synthesis of the A-F ring systems of YTX/ATX

Along their pursuit of total synthesis of YTX/ATX, Kadota and co-workers have synthesized three individual fragments, the A-F and F-I ring systems of YTX/ATX and the I-K ring system of YTX.[22] Central to their synthesis of the A-F and F-I fragments is an intramolecular allylation of an α-acetoxy ether and ring-closing metathesis sequence on top of a convergent coupling strategy, while a linear approach was employed in their synthesis of the I-K fragment of YTX.

The convergent synthesis of the A-F ring system from Kadota's laboratory is shown in Figure 3.5. Both coupling partners were synthesized from 2-deoxy-D-ribose (**3.5**). Yamaguchi esterification was used to couple the two fragments to give ester **3.25**, which in five steps was converted into allyl stannane **3.26**. Half reduction of the ester and a subsequent quench with chloroacetic anhydride gave stannyl α-acetoxy ether **3.27**, which upon treatment with BF_3•OEt_2, afforded the D ring of YTX/ATX **3.28** as a single stereoisomer. Subsequent ring-closing metathesis using Grubbs' 1st generation catalyst **3.29** furnished the E ring and completed the synthesis of the A-F ring system of YTX/ATX **3.30**. Kadota's synthesis of the F-I ring system of YTX/ATX adopted the same coupling strategy as in the A-F ring system, and their synthesis of the I-K ring system is reminiscent of Nakata's synthesis of the D-F ring system that has been described earlier.[20]

Oishi's Synthesis of the A-J Ring System of YTX

The first report towards the synthesis of YTX/ATX from Oishi's group appeared in 2005, which described their synthesis of the F-I ring system.[23a] They have followed up

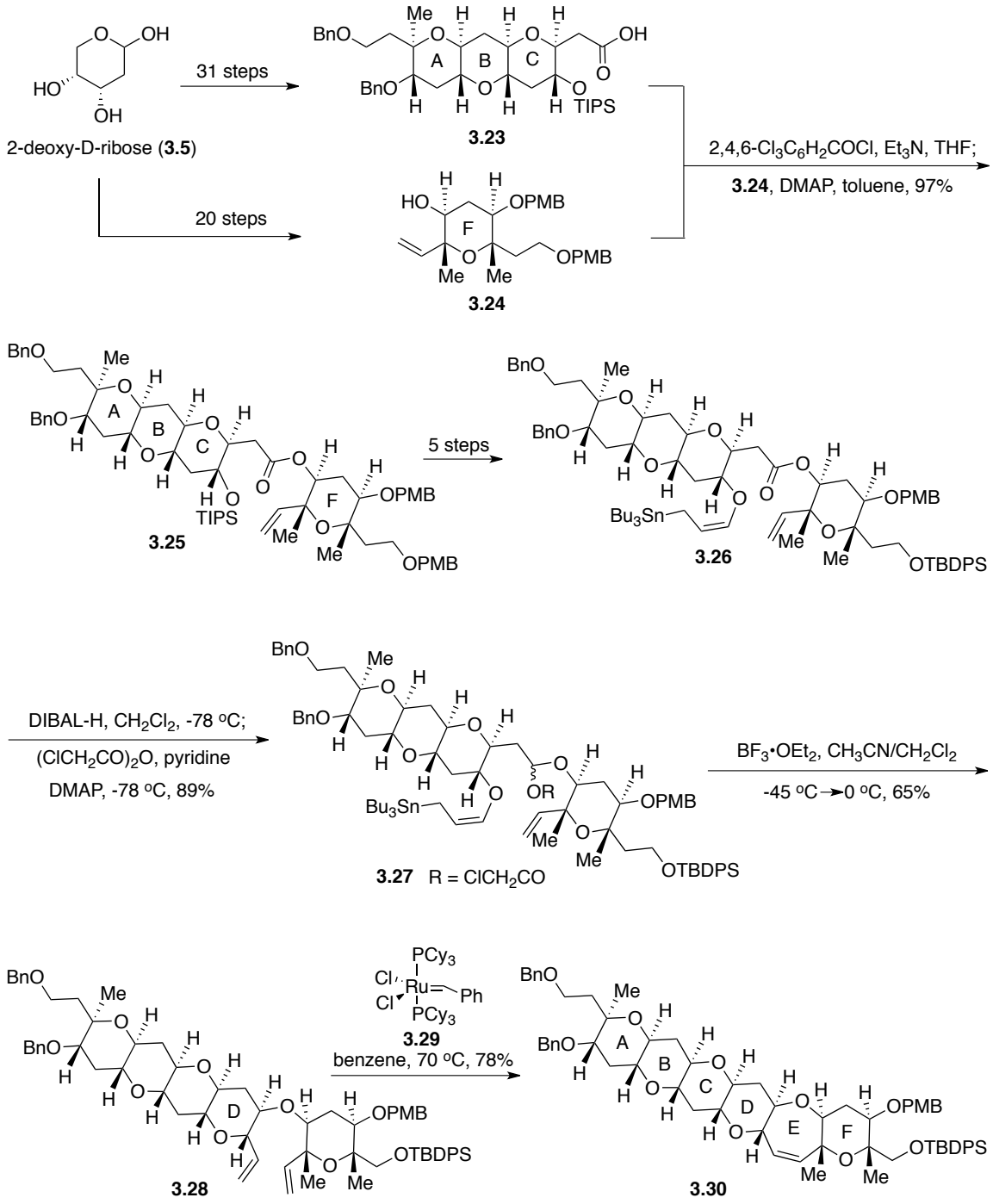


Figure 3.5. Kadota's synthesis of the A-F ring system of ATX

with their syntheses of the A-C and C-F of YTX/ATX together with the IJ and JK ring system of YTX.[23b-d] In 2008, they managed to put these fragments together to achieve the synthesis of the A-J ring system of YTX, which consists of all the ring structures of ATX and is only one ring short from the ring structure of YTX.[23e] The retrosynthetic analysis is shown in Figure 3.6. Oishi and co-workers have proposed a highly convergent strategy utilizing their α-cyano ether methodology based on the coupling between A-C ring aldehyde **3.32** and F-J ring diol **3.33**. Diol **3.33** in turn would be obtained from the F

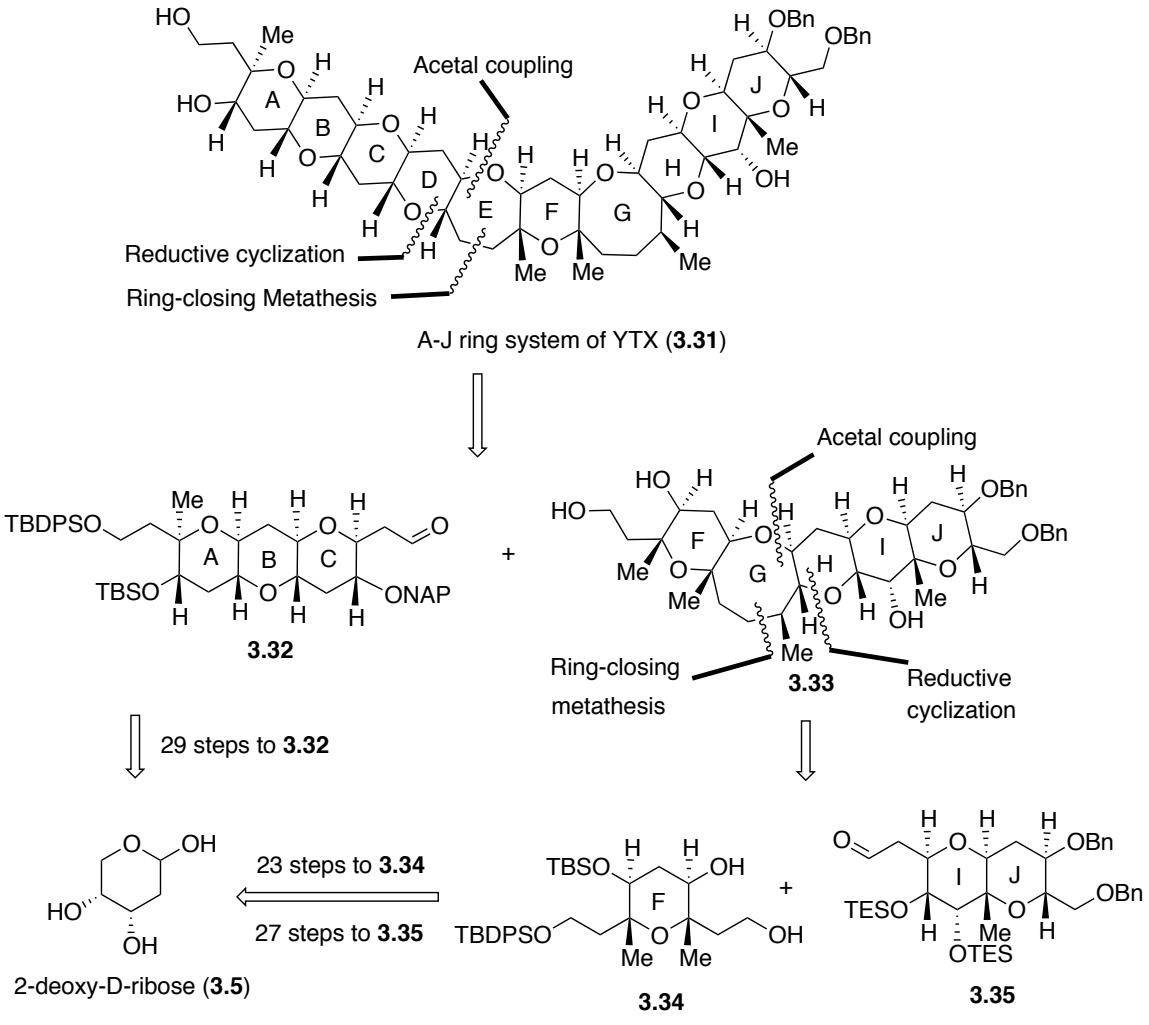


Figure 3.6. Oishi's retrosynthetic analysis of the A-J ring system of YTX

ring diol **3.34** and the IJ ring aldehyde **3.35** using the same methodology. Interestingly, all of the three building blocks could be generated from 2-deoxy-D-ribose (**3.5**).[23b,c,26]

The coupling of diol **3.34** and aldehyde **3.35** was achieved using $Sc(OTf)_3$ to give the cyclic acetals as a diastereomeric mixture at C28 (Figure 3.7). Regioselective opening of the acetals using TMSCN and $Sc(OTf)_3$ afforded α-cyano ether **3.37**, which was converted into aldehyde **3.38** in three steps. Vinyl addition to **3.38** generated diene **3.39** as a mixture of four diastereomers. When **3.39** was subjected to Grubbs' 2nd generation catalyst **3.40**, the eight-membered G ring of YTX was formed successfully. The mixture of diastereomers was subsequently converted into one single compound **3.42** after four steps. After a stereoselective methylation at C26, an impressive reductive cyclization from the TES-protected hydroxy ketone successfully afforded the H ring. Removal of the silyl protecting groups then furnished the F-J ring coupling parnter **3.33**.

The $Sc(OTf)_3$-promoted coupling between A-C ring aldehyde **3.32** and F-J ring diol **3.33** proceeded smoothly to give cyclic acetal **3.43**, which was then converted into α-cyano ether **3.44** as a diastereomeric mixture at C15 (Figure 3.8). Using the same strategy as before, **3.44** was converted into diene **3.45** in five steps. Ring-closing metathesis with Grubbs' 2nd generation catalyst **3.40** successfully afforded the E ring of YTX, which after oxidation, hydrogenation, and equilibration at C15 furnished the ketone **3.46** as a single compound. Finally, removal of the NAP group, reductive cyclization, and deprotection of the silyl groups gave the A-J ring system of YTX **3.31**.

Oishi's synthesis of the A-J ring system of YTX is highly convergent and has demonstrated the power of their α-cyano ether methodology in the synthesis of polycyclic ether natural products.

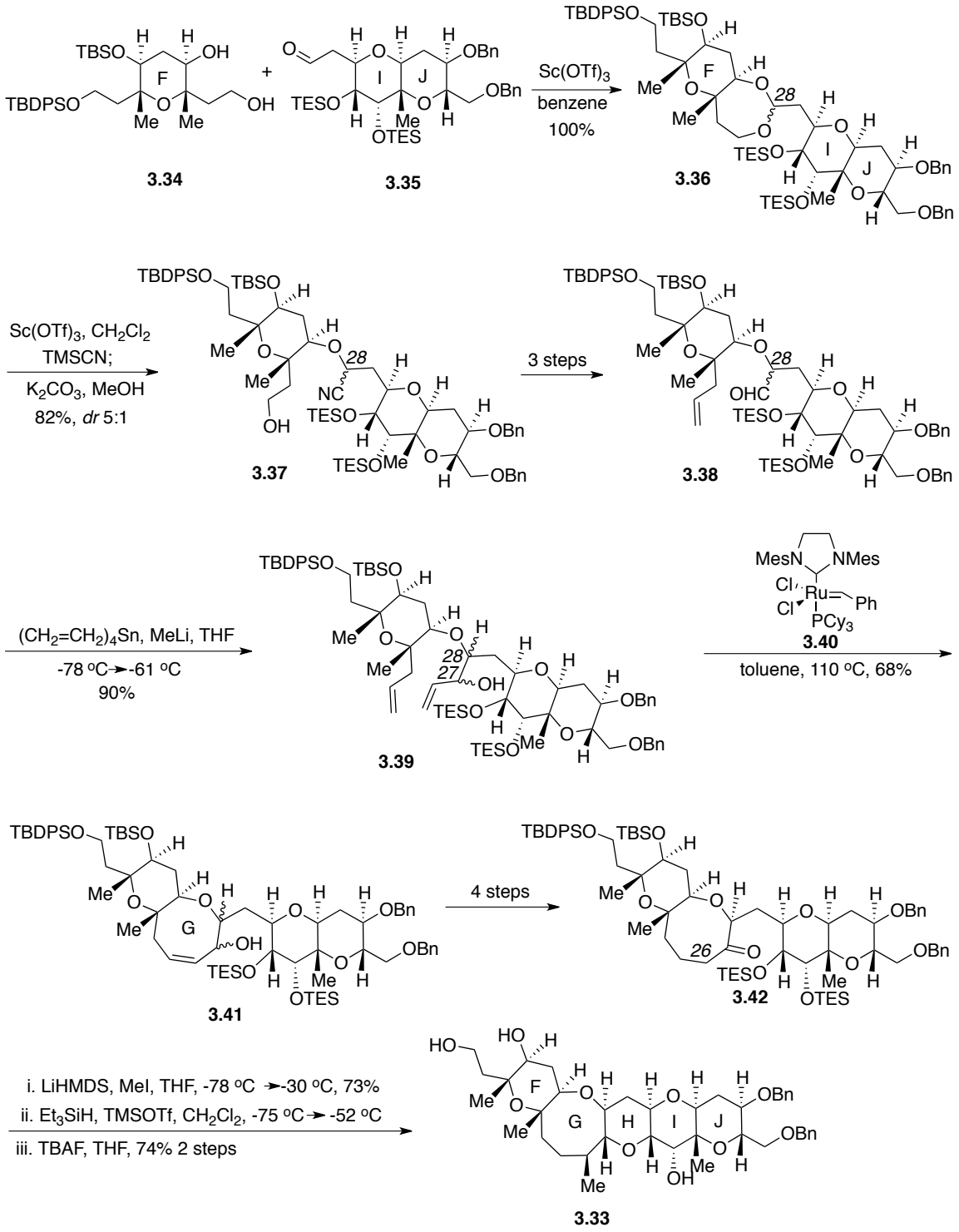
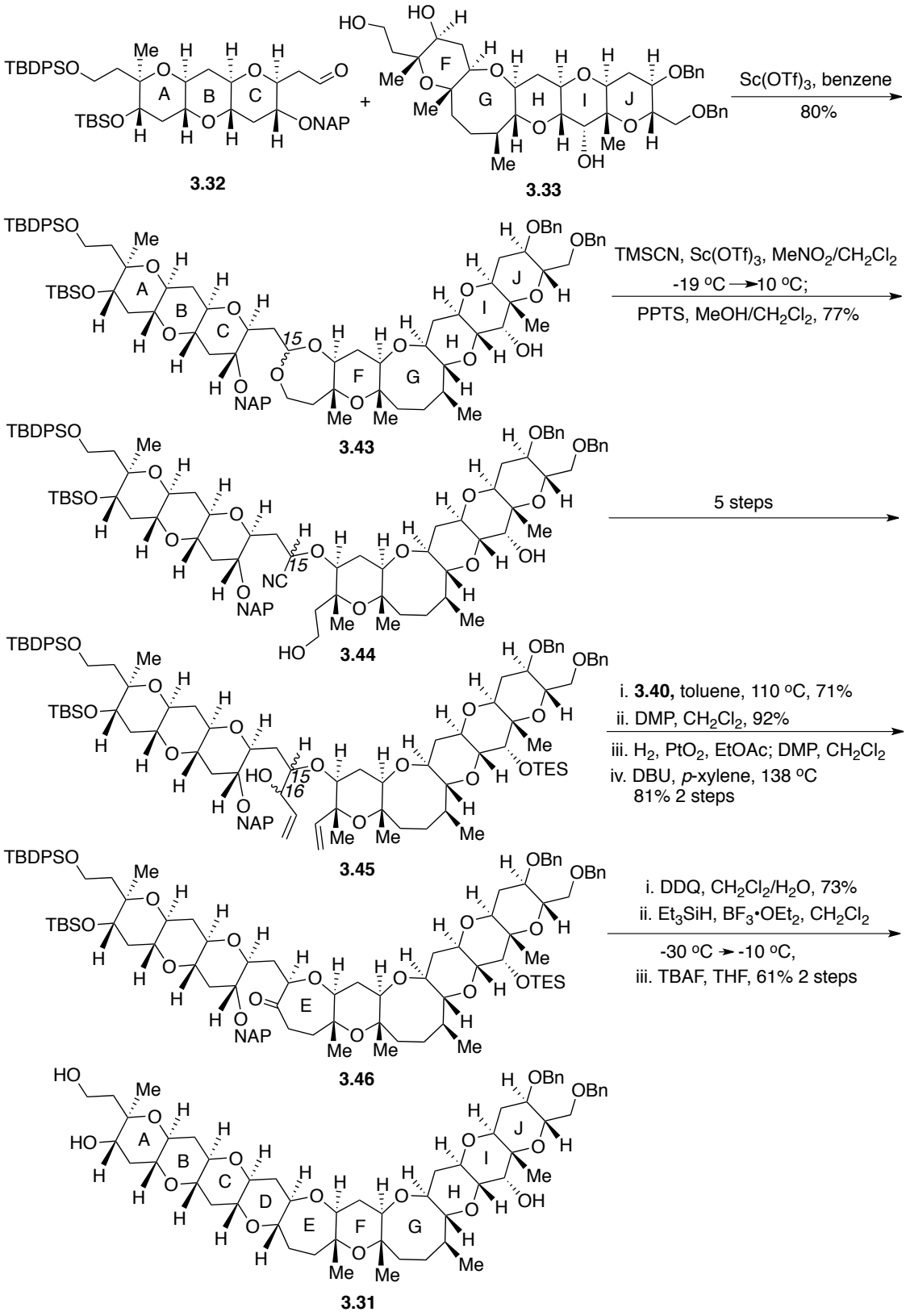


Figure 3.7. Oishi's synthesis of the F-J ring system of ATX



3.32 + 3.33 → 3.43 → 3.44 → 3.45 → 3.46 → 3.31

Figure 3.8. Oishi's synthesis of the A-J ring system of ATX

Results and Discussions

As mentioned earlier, as a starting point of our synthetic program toward YTXs, we chose ATX as our synthetic target since it represents a truncated and simplified analogue of YTX. Even so, ATX is still a very challenging synthetic target considering its decacyclic *trans*-fused polyether ring system, 24 stereocenters, and 4 angular methyl groups. Thus at the outset of our synthesis of ATX, we realized that a convergent strategy had to be used due to its structural complexity. Shown in Figure 3.9 is our retrosynthetic analysis of ATX.

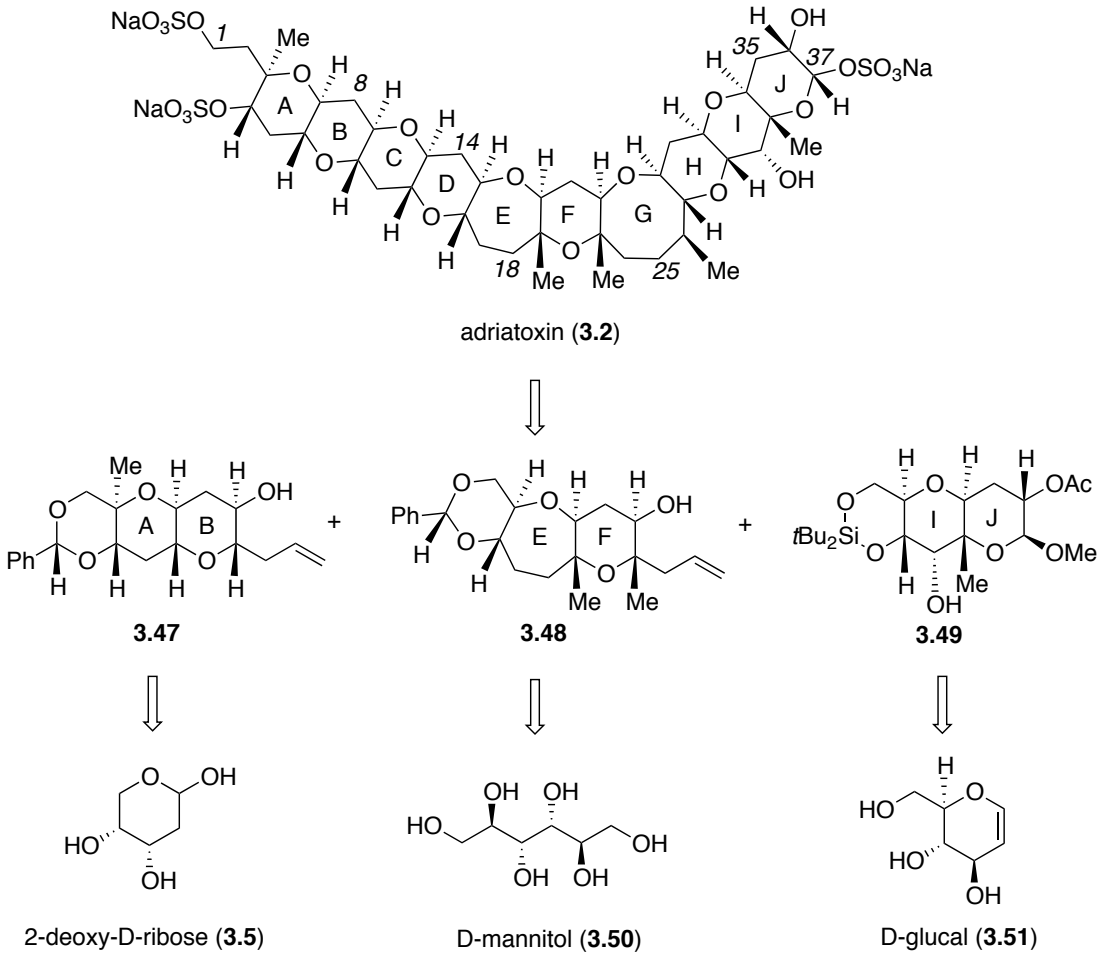


Figure 3.9. Retrosynthetic analysis of ATX

We envisioned that ATX would come from the coupling of three bicyclic substructures of similar size **3.47**, **3.48**, and **3.49**, representing the AB, EF, and IJ ring fragments respectively. Based on the coupling strategy shown in Figure 1.21, we expect that two additional rings will be generated after pairing of two subunits. Because of the lynchpin nature of the EF ring system, the structure of **3.48** is designed in a way that both sides are properly functionalized and can be flexibly modified to couple with either AB or IJ ring systems. All of the three subunits **3.47**, **3.48**, and **3.49** can be obtained from simple saccharides, and their syntheses have been previously carried out by Dr. Clement Akoto from our group.[31c]

Synthesis of the AB Ring Fragment **3.47**

Our synthesis of the AB ring fragment of ATX **3.47** commenced from 2-deoxy-D-ribose (**3.5**, Figure 3.10), which was converted into triol **3.52** using a Wittig olefination.[32] The two stereocenters in 2-deoxy-D-ribose were transferred to become C3 and C4 on the A ring of ATX. Selective protection of two of the three hydroxy groups was achieved using $PhCH(OMe)_2$ to afford the secondary alcohol **3.53**, which was subsequently oxidized to give ketone **3.54** using Swern's conditions.[33] A stereoselective methyl Grignard addition to the ketone generated tertiary alcohol **3.55**, which was coupled with known acid **3.56**[34] to give ester **3.57**. When **3.57** was subjected to our modified Takai-Utimoto reaction conditions using dibromoethane as the titanium alkylidene source, olefinic ester cyclization proceeded smoothly to generate the A ring of ATX as cyclic enol ether **3.58**.[35]

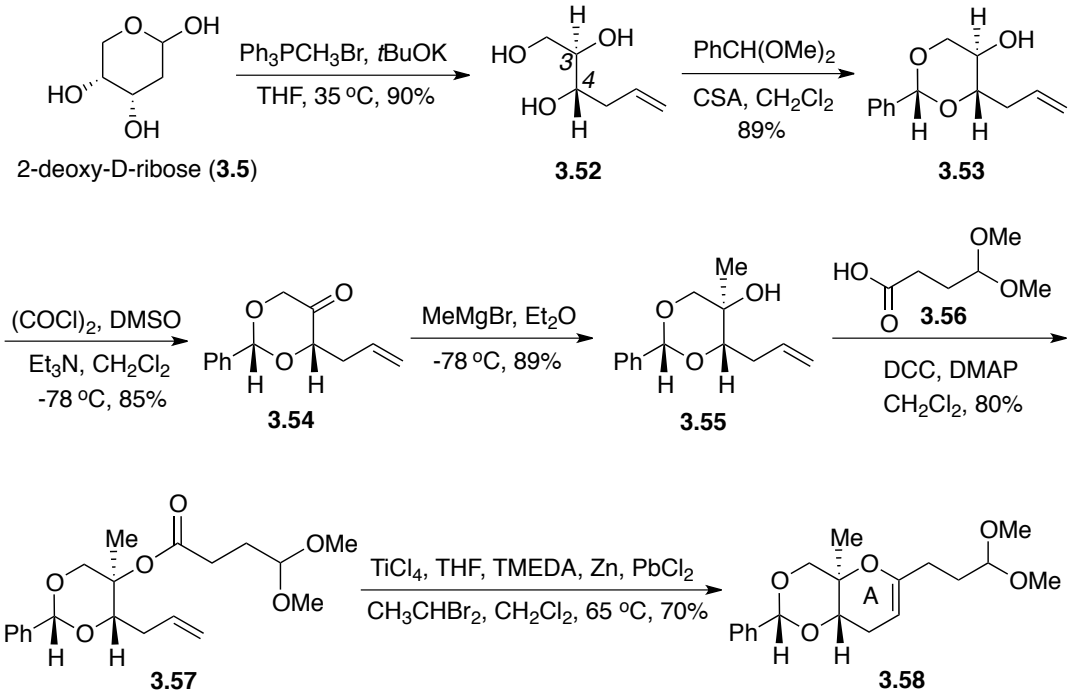


Figure 3.10. Synthesis of the A ring of ATX

With the A ring in hand, the stereochemistry at C7 was set utilizing a Lewis acid promoted pinacol-type rearrangement (Figure 3.11).[28] A stereoselective oxidation of enol ether **3.58** with DMDO directed by the presence of the C3 methyl group afforded epoxide **3.59**. When the resulting epoxide **3.59** was subjected to $MgCl_2$, oxocarbenium ion **3.60** was presumably formed, which underwent a *syn*-facial [1,2]-hydride shift to give ketone **3.61** as a single stereoisomer. It is noteworthy that because of the presence of the C3 methyl group, either hydroboration or the DMDO/*i*Bu_2AlH protocol would give the undesired stereochemistry at C7.

The ketone obtained in the rearrangement was subsequently reduced using $NaBH_4$ to generate secondary alcohol **3.62**, which upon treatment with PPTS and pyridine in

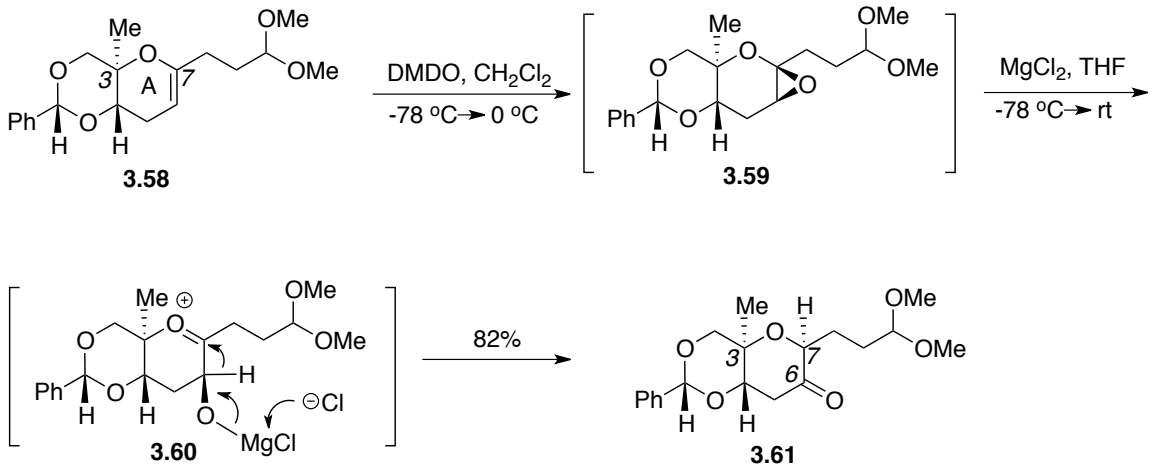


Figure 3.11. Pinacol-type rearrangement to set C7 stereochemistry

refluxing chlorobenzene, was converted into enol ether **3.63** with the formation of the B ring of ATX(Figure 3.12).[27,36]

Treatment of enol ether **3.63** with DMDO and subsequent allyl addition to the resulting epoxide generated a 2.3:1 mixture of secondary alcohols favoring the desired AB ring coupling precursor **3.47**. Though the selectivity was low, the undesired stereoisomer **3.64** could be recycled and converted into **3.47** using a three-step sequence involving oxidation, equilibration of the C9 stereocenter, and subsequent reduction. Thus, the functionalized AB ring system of ATX **3.47** was obtained in 13 steps from 2-deoxy-D-ribose (**3.5**), which also serves as the only chirality source of the AB subunit.

Synthesis of the EF Ring Fragment **3.48**

The synthesis of the EF ring system **3.48** commenced from D-mannitol (**3.50**), which was converted to D-glyceraldehyde acetonide **3.65** in two steps (Figure 3.13). The

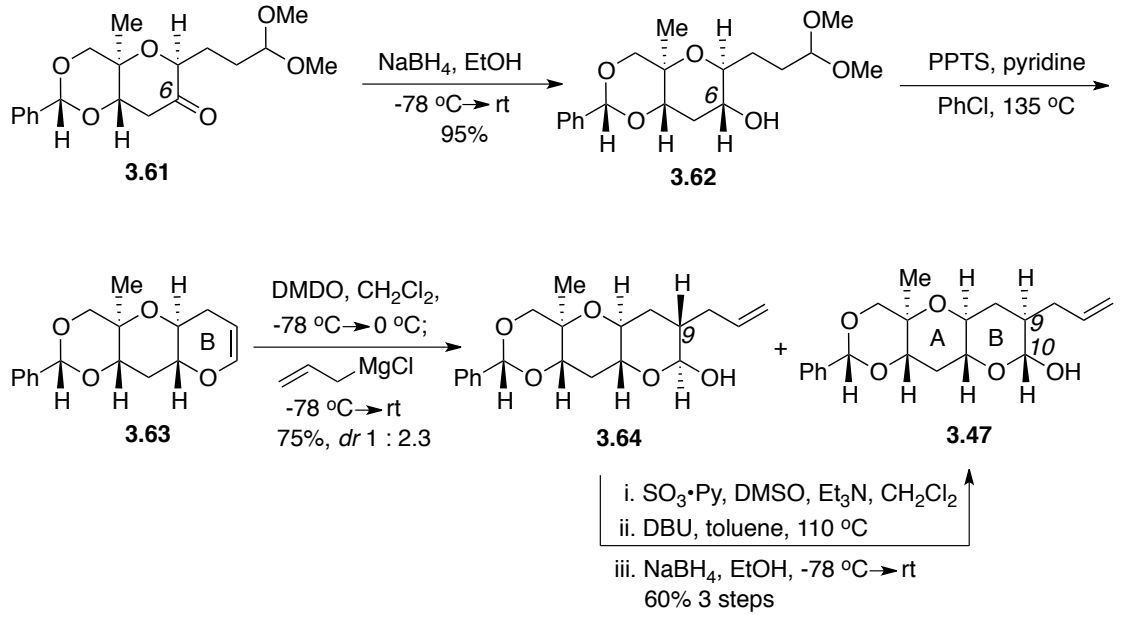


Figure 3.12. Synthesis of the AB ring fragment of ATX

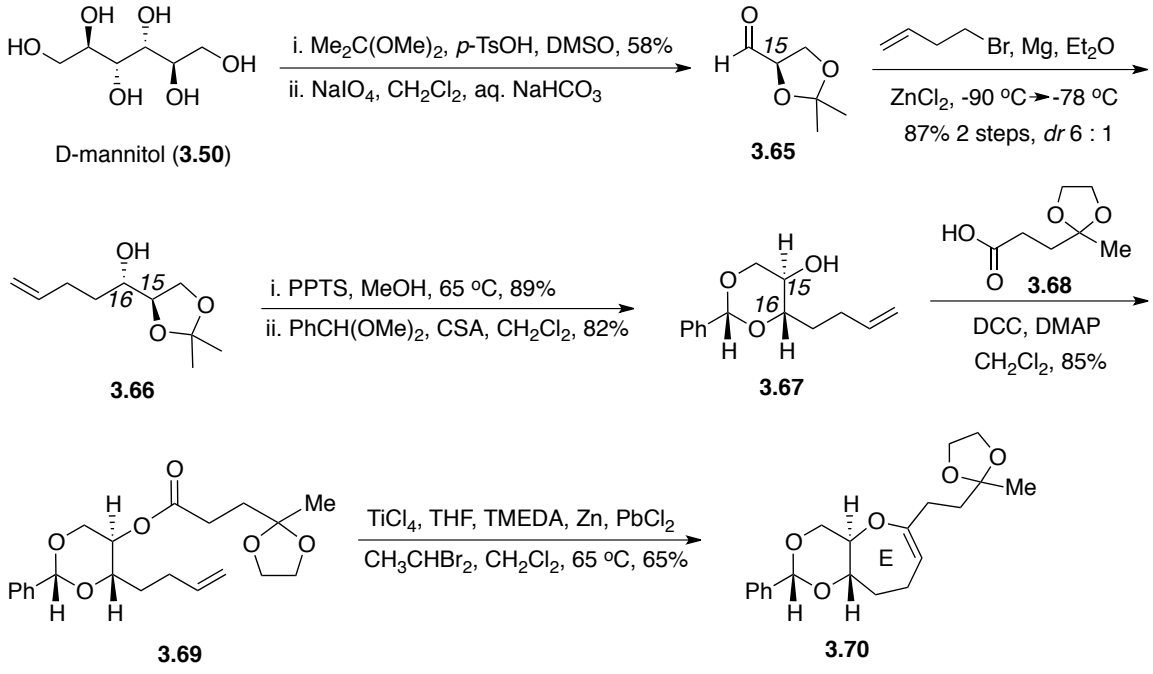


Figure 3.13. Synthesis of the E ring of ATX

stereocenter in **3.65** would become the C15 of ATX. A chelation-controlled homoallylic Grignard addition to the aldehyde in the presence of $ZnCl_2$ gave a 6:1 diastereomeric mixture favoring secondary alcohol **3.66**, which was converted into **3.67** after removal of the acetonide and benzylidene protection. Secondary alcohol **3.67** was subsequently coupled with known acid **3.68**[37] to give ester **3.69**, which when subjected to the reduced titanium ethylidene reagents, underwent olefinic ester cyclization to furnish the E ring of ATX as cyclic enol ether **3.70**.

With the E ring enol ether in hand, oxidation with DMDO and in situ reduction of the resulting epoxide with *i*Bu_2AlH afforded secondary alcohol **3.71** as a single stereoisomer (Figure 3.14).[38,39] Alcohol **3.71** was subsequently oxidized to ketone **3.72**, which upon treatment with the methyl Grignard reagent, afforded a 5:1 mixture of diastereoisomers favoring the desired tertiary alcohol **3.73**. When **3.73** was subjected to PPTS and pyridine in refluxing chlorobenzene, an acid-promoted cyclization proceeded smoothly to give the F ring of ATX as cyclic enol ether **3.74**.

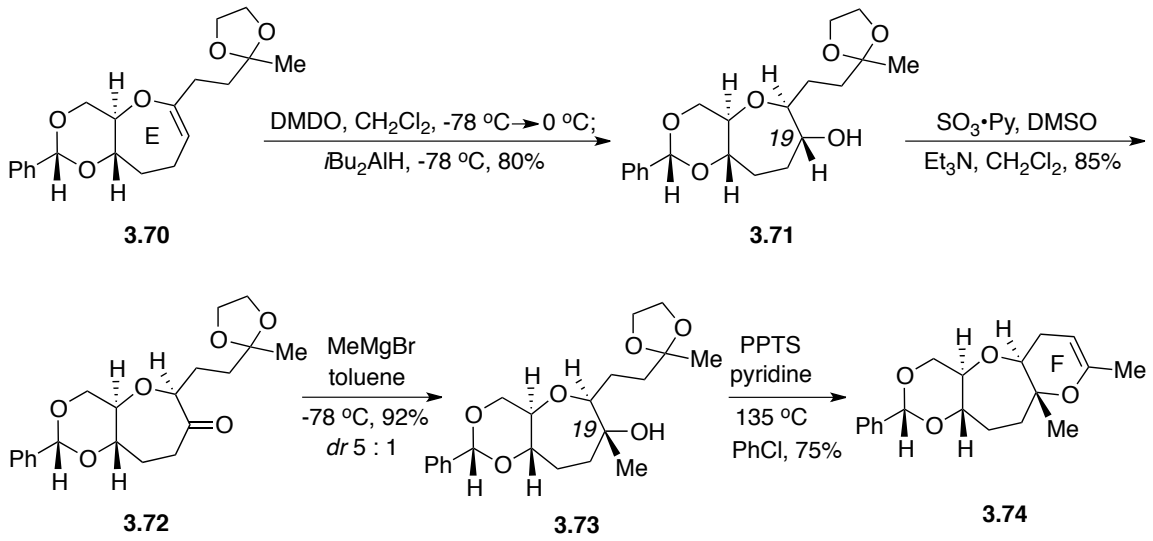


Figure 3.14. Synthesis of the F ring of ATX

To convert **3.74** to the desired EF ring fragment **3.48**, a Claisen rearrangement was exploited to install the required stereochemistry (Figure 3.15).[29,31c] Stereoselective epoxidation of the enol ether **3.74** directed by the C19 methyl group generated hydroxy ketal **3.75** as a 6:1 mixture at the anomeric C23. Subsequent allylation afforded **3.76**, which upon treatment with PPTS and pyridine in refluxing toluene, was converted into ketone **3.78** with high yield and excellent stereoselectivity presumably through the allyl vinyl ether intermediate **3.77**. The stereoselectivity in the Claisen rearrangement is believed to be a result of the allyl group adding from the face opposite to the C19 angular methyl group.[29] Because of the presence of the C19 methyl group, the use of DMDO and allyl Grignard would have given the undesired stereochemistry at C23. Reduction of the ketone in **3.78** afforded the desired EF ring coupling precursor **3.48**. The functionalized EF ring system **3.48** was synthesized in 15 steps from D-mannitol (**3.50**), which was the only source of stereocenters.

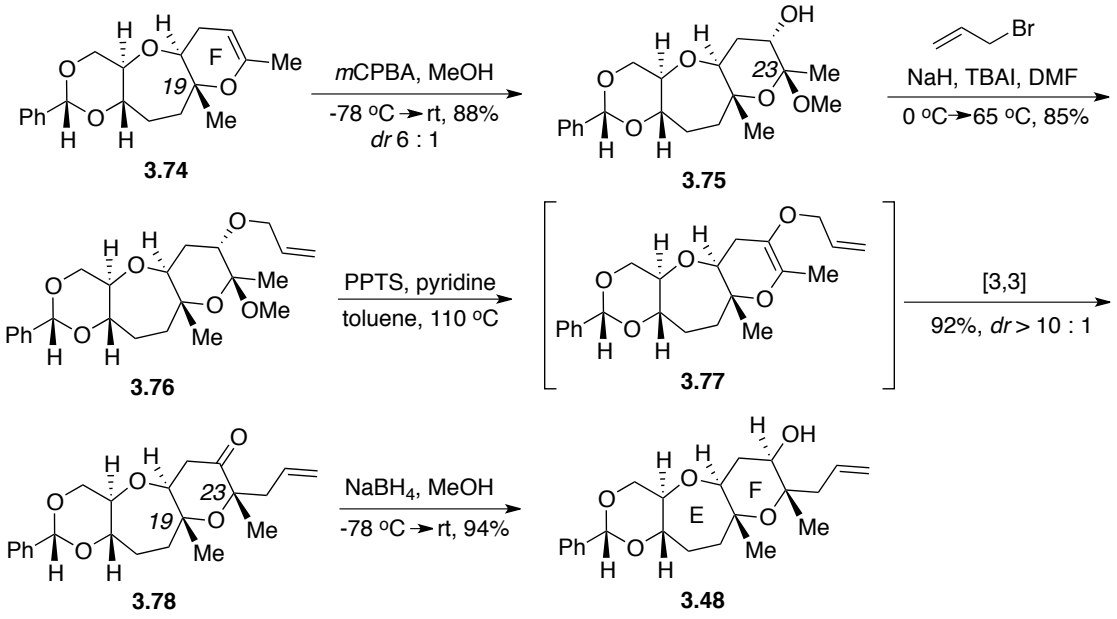


Figure 3.15. Synthesis of the EF ring fragment of ATX

Synthesis of the IJ Ring Fragment **3.49**

Our synthesis of the IJ ring fragment **3.49** commenced from D-glucal (**3.51**, Figure 3.16). We envisioned that the pyran ring in **3.51** would become the I ring of ATX. Sequential silylene and benzyl ether formation afforded enol ether **3.79**, which was subjected to a stereoselective DMDO oxidation directed by the C32 benzyl ether. The resulting epoxide was then treated with allyl Grignard reagent to give secondary alcohol **3.80** as a single stereoisomer.[40] After oxidation of alcohol **3.80**, methyl addition to the resulting ketone **3.81** using MeLi gave a 7:1 mixture favoring the desired tertiary alcohol **3.82**. To make the J ring, the tertiary alcohol on C33 was converted into a vinyl ether, which when subjected to Grubbs' 2nd generation catalyst **3.40**, underwent ring-closing metathesis to give the J ring enol ether **3.84**.

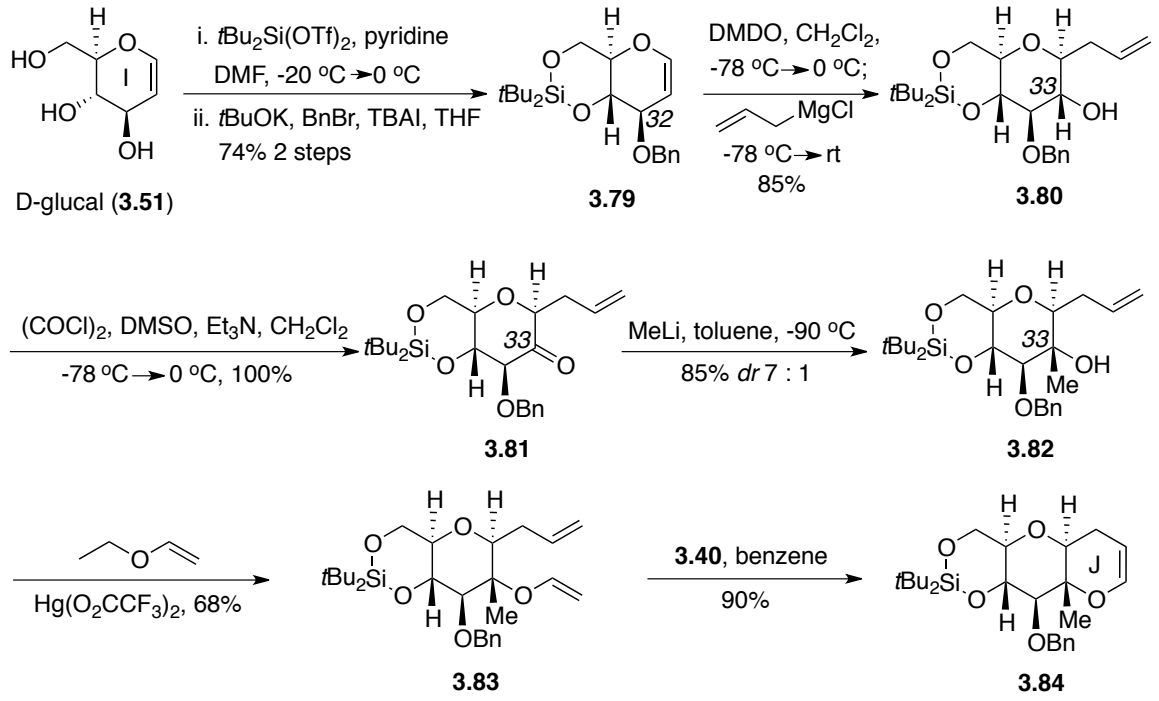


Figure 3.16. Synthesis of the J ring of ATX

With the J ring in place, we were ready to complete the synthesis of the IJ ring system **3.49**. A stereoselective epoxidation of the enol ether **3.84** with *m*CPBA directed by the C33 angular methyl group and subsequent ring opening of the resulting epoxide with methanol afforded acetal **3.85** as a 6:1 mixture at the anomeric position (Figure 3.17). The resulting C36 alcohol was subsequently protected as the corresponding acetate **3.86**. We believe that the C37 methyl acetal can be epimerized at a late stage in the synthesis of ATX.

In order to synthesize the desired IJ ring coupling precursor, the stereocenter at C32 had to be inverted. To that end, the benzyl group was removed under hydrogenolysis conditions and the resulting alcohol was oxidized to the corresponding ketone **3.88**. Reduction with L-selectride successfully afforded the desired stereocenter at C32 through equatorial hydride delivery. The IJ ring fragment of ATX **3.49** was synthesized from D-glucal in 12 steps. As with the other precursors, substrate control had been used to generate the IJ ring stereocenters.

With the synthetic routes to the precursors established, we were able to obtain sufficient quantities of the AB, EF, and IJ ring systems of ATX and study the coupling chemistry. As mentioned earlier, the EF ring system in our retrosynthetic analysis acts as a lynchpin to connect the AB and IJ fragments. As the EF ring system **3.48** is properly functionalized for orthogonal coupling, we chose to initially test the coupling of the AB/EF and the EF/IJ fragments individually.

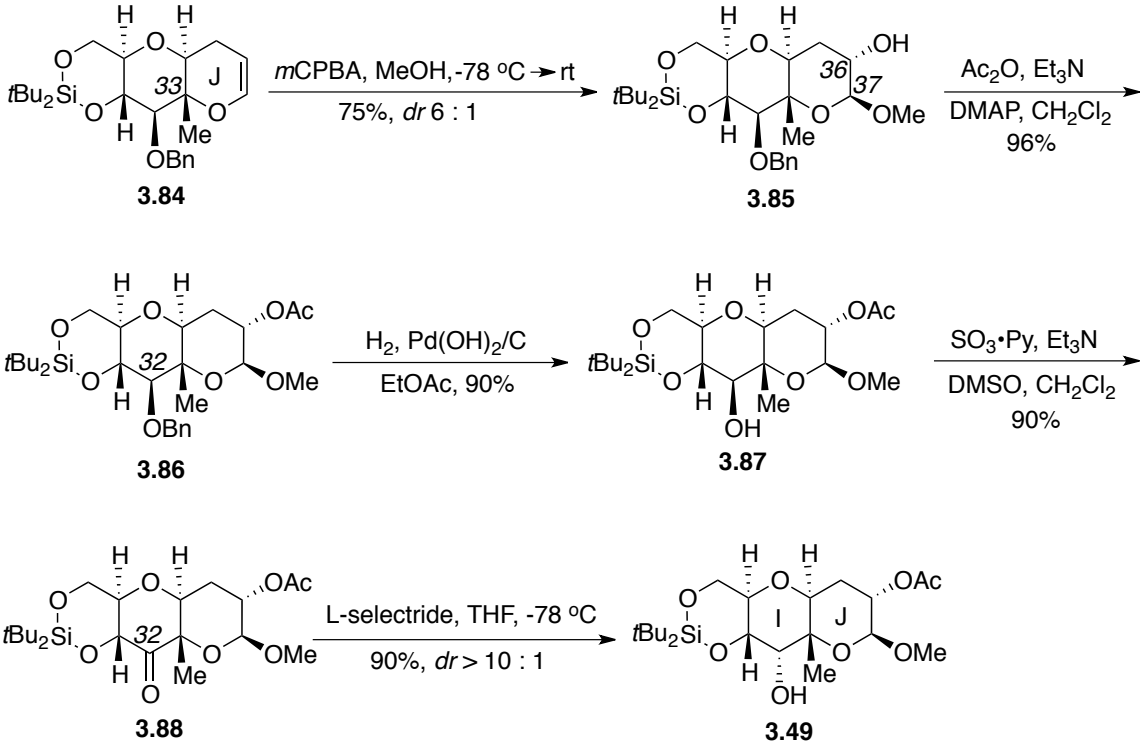


Figure 3.17. Synthesis of the IJ ring fragment of ATX

Synthesis of the A-F Ring System of ATX

As outlined in Figure 1.21, our proposed coupling strategy would involve an esterification between an acid and an alcohol. To meet this need, both structures of the obtained AB ring system **3.47** and the EF ring system **3.48** require modification.

We decided to convert the AB fragment into acid **3.91**, while the EF fragment would be converted into alcohol **3.98**. To this goal, the secondary alcohol in **3.47** was protected as a TBS ether (Figure 3.18). Ozonolysis of the terminal alkene afforded aldehyde **3.90**, which was oxidized using Pinnick's conditions to afford the AB ring coupling partner **3.91**.[41]

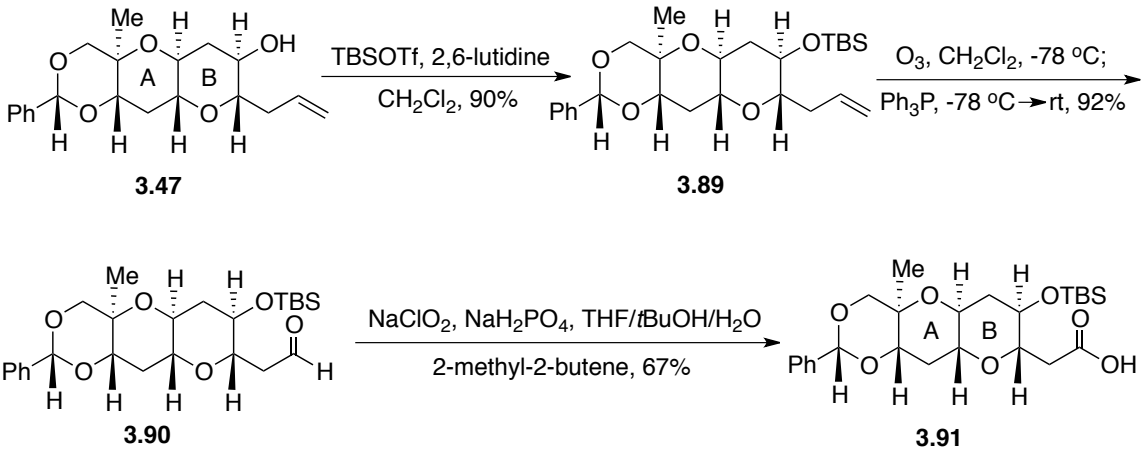


Figure 3.18. Synthesis of the AB coupling partner **3.91**

The synthesis of alcohol **3.98** began with a PMB ether formation of the secondary alcohol in **3.48** (Figure 3.19). Ozonolysis of the terminal alkene followed by reduction of the resulting aldehyde gave primary alcohol **3.93**, which was subsequently protected as a benzyl ether. The benzylidene protecting group on the E ring was removed using CSA in methanol to give diol **3.94**. Using a one-pot procedure, the primary alcohol in **3.94** was converted into a triflate, and the secondary alcohol was protected as TBS ether. When triflate **3.95** was subjected to lithium trimethylsilylacetylide, the primary triflate was substituted to afford internal alkyne **3.96**. After removal of both silyl protecting groups, partial hydrogenation using Lindlar's catalyst in the presence of quinoline gave the EF ring coupling precursor **3.98**.[42]

With both precursors in hand, we set out to test our coupling strategy (Figure 3.20). Esterification between acid **3.91** and alcohol **3.98** proceeded smoothly under Yamaguchi's conditions to give **3.99**.[43] Once the olefinic ester **3.99** was subjected to our modified Takai-Utimoto reaction conditions using dibromoethane,[35] cyclic enol ether **3.100** was isolated as the only product in 50% yield. The product appears to be unstable

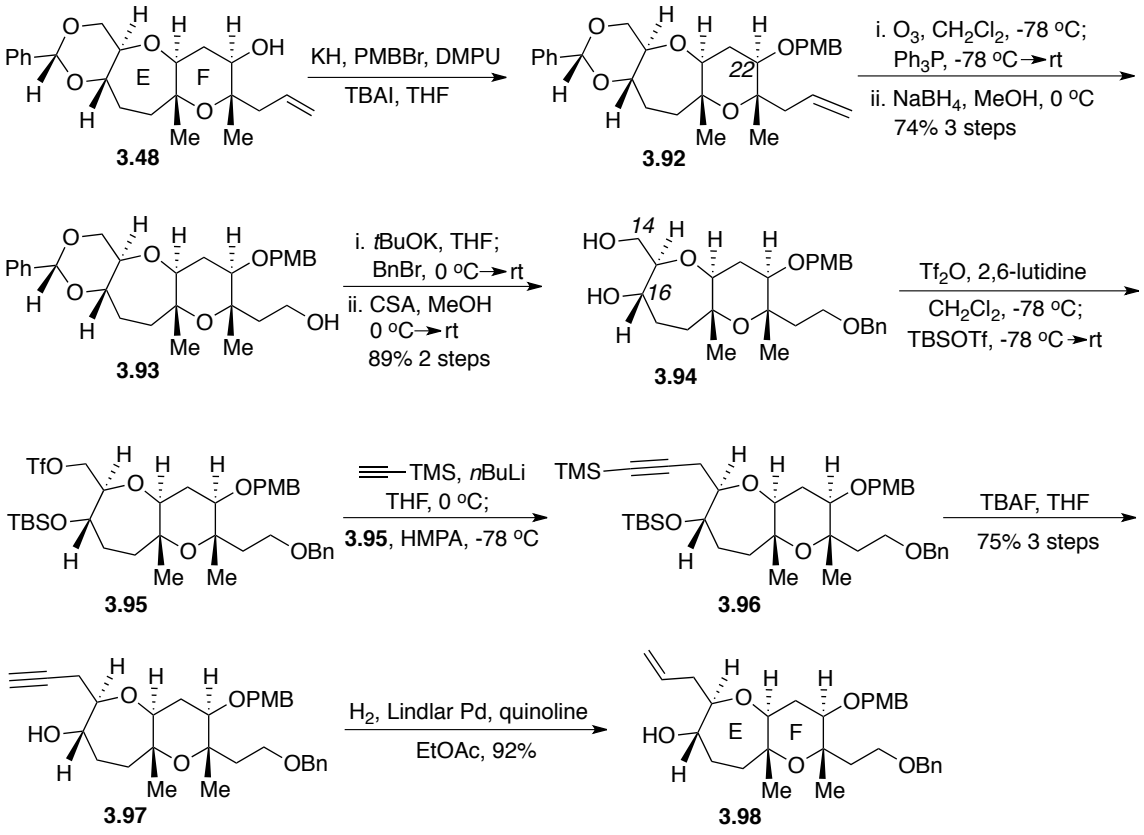


Figure 3.19. Synthesis of the EF ring coupling partner **3.98**

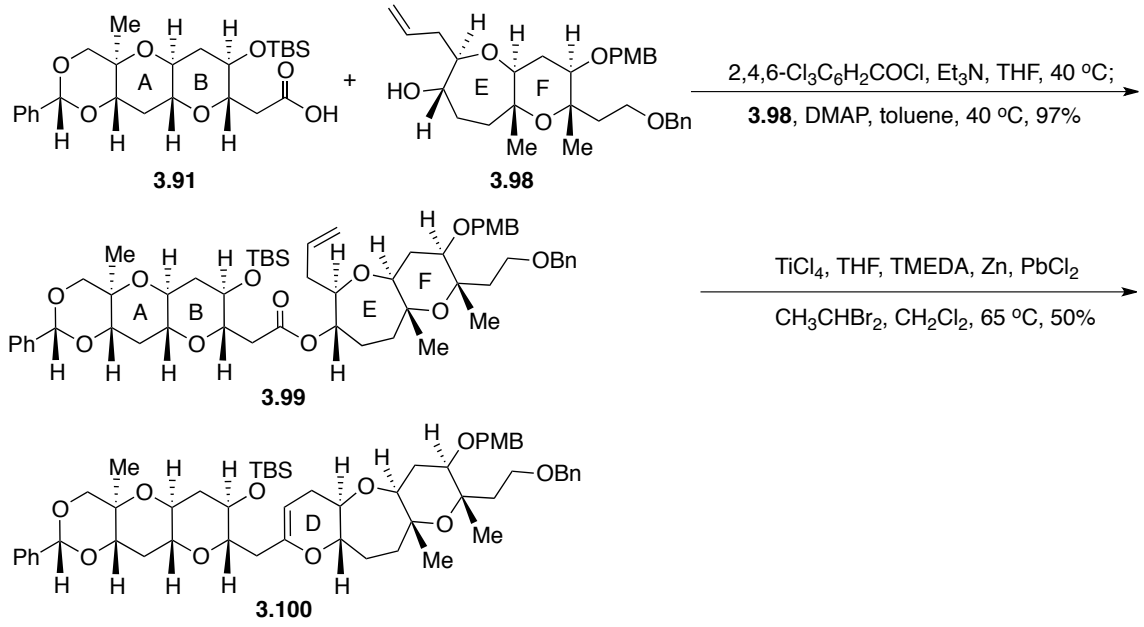


Figure 3.20. Synthesis of the D ring of ATX

under the reaction conditions and the reaction has to be quenched as soon as the starting material disappears. Significantly diminished yields were observed when the reaction was allowed to proceed for a logner periods of time.

With the D ring in hand, DMDO oxidation of enol ether **3.100** and in situ reduction of the resulting epoxide with *i*Bu_2AlH afforded a separable 3:1 mixture of diastereomers favoring alcohol **3.101** that had the desired stereochemistry at C12 and C13 (Figure 3.21). The stereochemical outcome of this reaction was confirmed by ^{1}H NMR ^3J values after converting the obtained secondary alcohol **3.101** into the corresponding acetate **3.102**. The diastereomeric alcohols from the DMDO/*i*Bu_2AlH

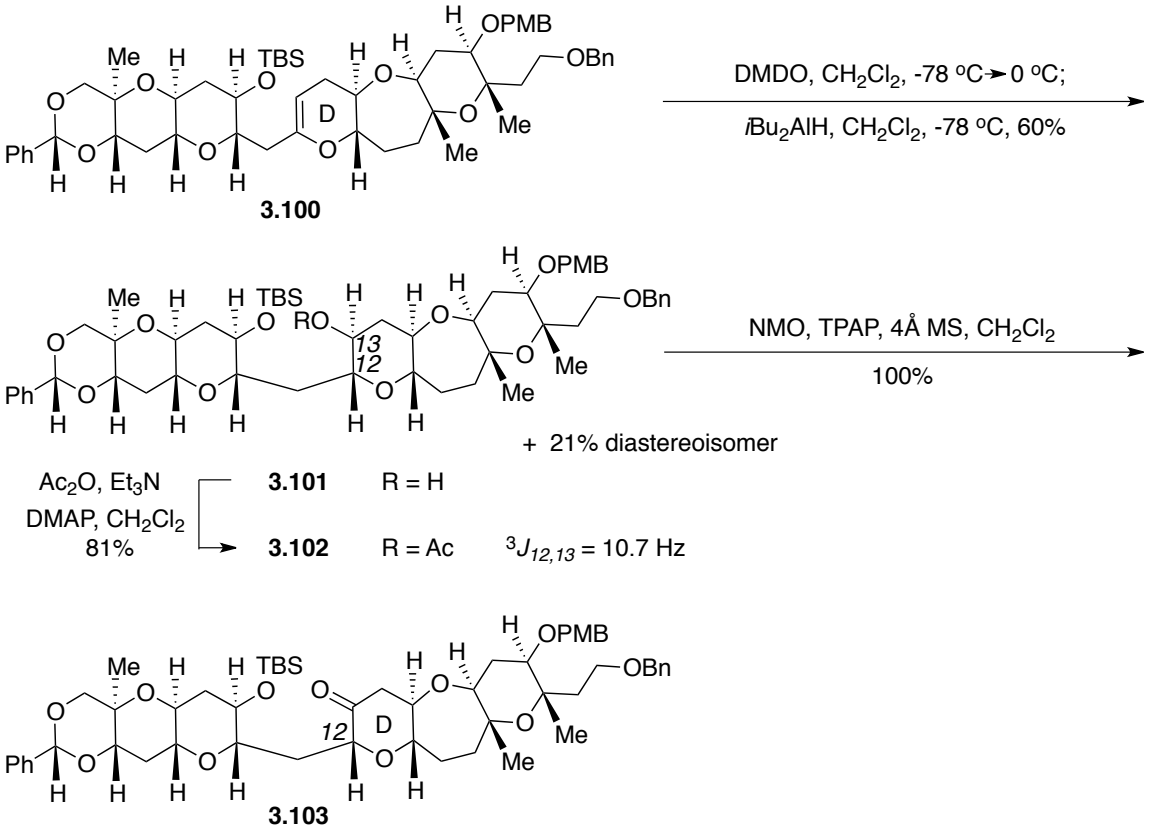


Figure 3.21. Functionalization of the D ring of ATX

step were separated and subsequently oxidized to the corresponding ketones. At this stage, the minor diastereoisomer could be recycled and converted into the desired ketone **3.103** using DBU in refluxing toluene in 80% yield.

With ketone **3.103** in hand, we set out to generate the C ring (Figure 3.22). The TBS group was removed using HF•Py, and the resulting hydroxy group simultaneously cyclized onto the ketone on the D ring to give hemiketal **3.104**. The disappearance of the

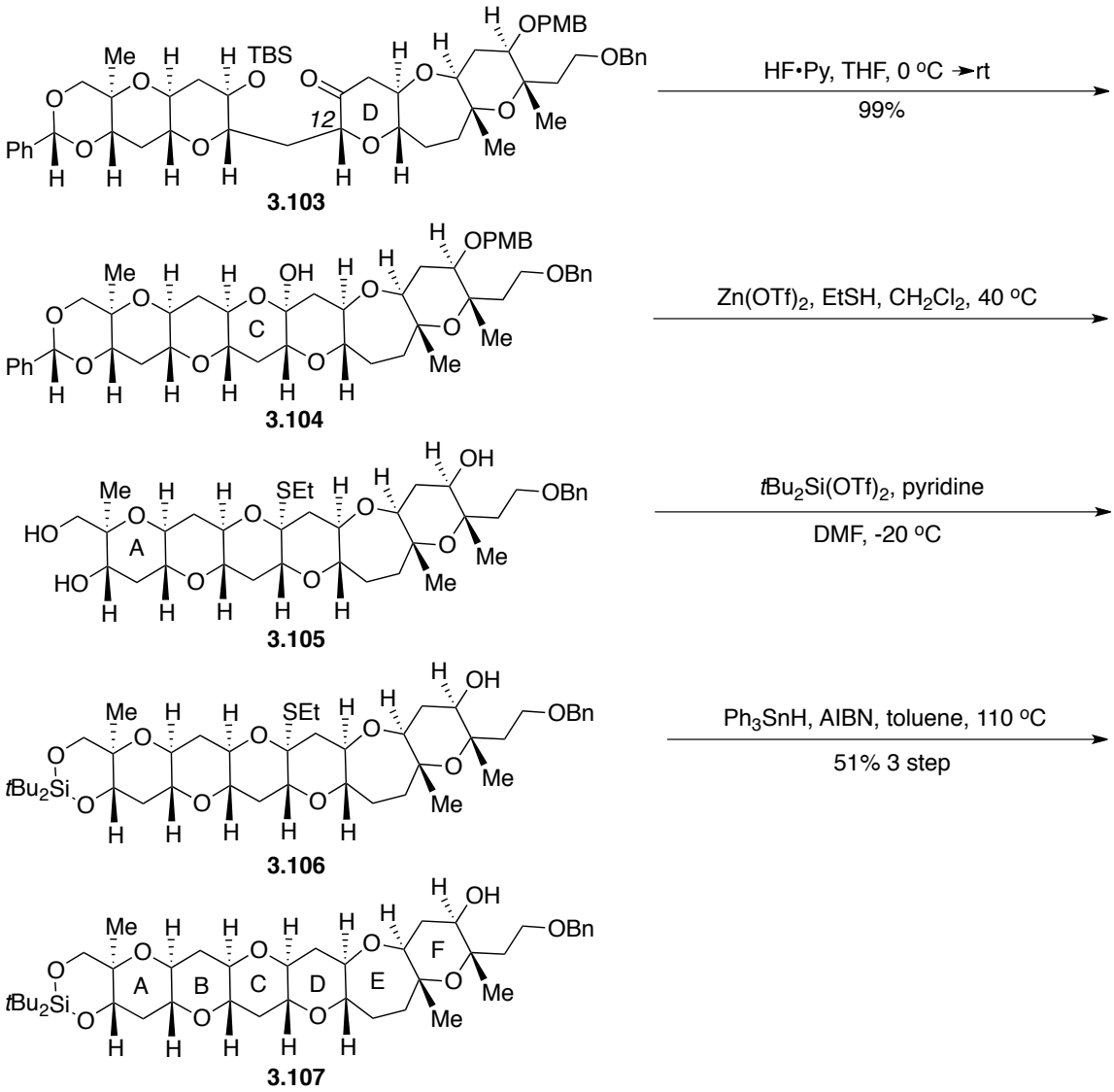


Figure 3.22. Synthesis of the A-F ring system of ATX

ketone signal in both ^{13}C NMR and IR supported this structure. Treatment of hemiketal **3.104** with $Zn(OTf)_2$ and EtSH in refluxing dichloromethane afforded *O,S*-mixed ketal **3.105** with concomitant removal of the benzylidene and the PMB protection groups. The two A-ring hydroxy groups were subsequently reprotected using a cyclic silylene group to give alcohol **3.106**. When **3.106** was subjected to Ph_3SnH and AIBN in refluxing toluene, we were pleased to find that the *O,S*-mixed ketal was successfully reduced to genaerate **3.107**, the hexacyclic A-F ring system of both ATX and YTX.

To summarize, we have successfully synthesized the A-F ring system of ATX and YTX using our highly convergent strategy. The highlights in the synthesis include a high-yielding esterification coupling step, a direct olefinic ester cyclization to generate the D ring, and an efficient radical reduction to make the C ring.

Synthesis of the F-I Ring System of ATX

When we set out to study the coupling of the EF and the IJ ring systems of ATX, we were aware of the difficulties associated with the formation of the eight-membered G ring. Based on the convergent coupling strategy shown in Figure 1.21, there were two options for us to construct the GH ring structure (Figure 3.23).

One would involve the initial use of olefinic ester cyclization to make the six-membered H ring followed by a reductive cyclization or mixed ketal radical reduction to form the eight-membered G ring. The advantage of this route is that six-membered ring formation from an olefinic ester cyclization was well documented and usually high yielding. The concerns about this approach were the stereoselective installment of the C26 methyl group and the feasibility of formation of the G ring. Although both Nicolaou

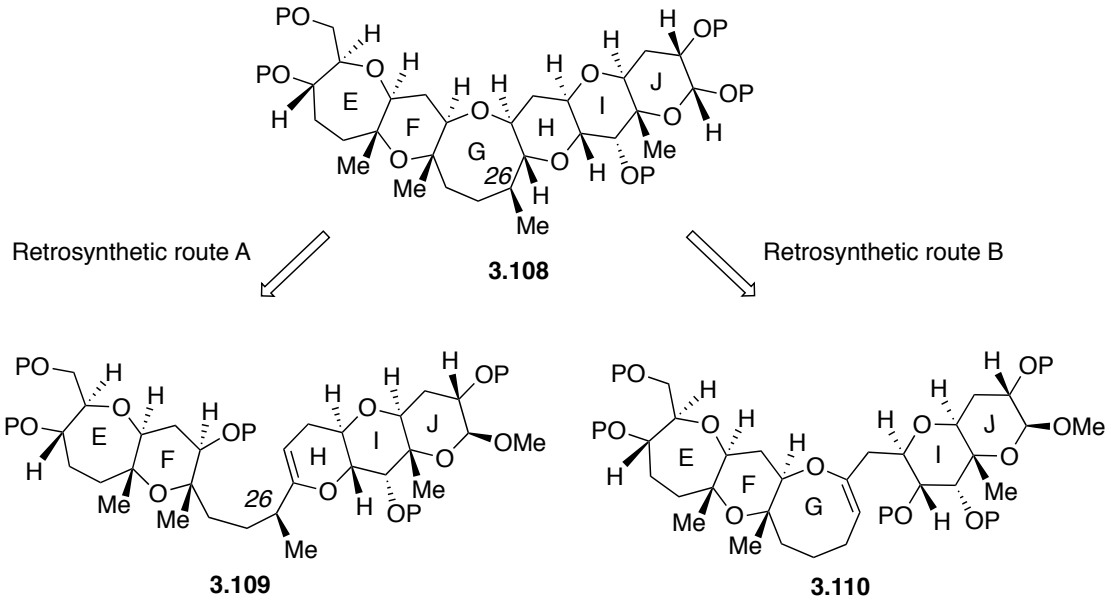


Figure 3.23. Synthetic options for E-J ring system of ATX

and Crimmins had generated related eight-membered ether ring structures in their syntheses of brevetoxin A, the presence of a *cis*-olefin in the backbone is always required to facilitate the cyclization.[44] To the best of our knowledge, cyclization of structures with saturated backbones such as **3.109** to generate eight-membered ether rings has not been reported.

The other option was to employ olefinic ester cyclization to form the eight-membered G ring, and a subsequent cyclization to generate the six-membered H ring. The concern with this approach was that there were no reports of eight-membered cyclic enol ether formations using olefinic ester cyclization or olefinic enol ether cyclization in the literature. In our unpublished work obtained by Dr. Jie Zhou,[45] we had demonstrated that eight-membered cyclic enol ethers could be successfully generated using our modified Takai-Utimoto protocol. However, the reaction was substrate-dependent and, not surprisingly, relied heavily on the space proximity between the olefin and ester motifs

in the substrate. In addition, the substrates that Dr. Zhou tested were significantly less complex than the substrate needed for the synthesis of ATX. Thus, it still remained a significant question as to whether the eight-membered G ring could be generated using an olefinic ester cyclization. On the other hand, if the proposed G ring formation were successful, the advantage of this route would include a possible stereoselective installment of the C26 methyl group under substrate control and a facile late-stage cyclization to make the six-membered H ring. It is for these reasons and the desire to push forward the development of the olefinic ester cyclization methodology that we opted to pursue the second approach for the synthesis of the E-J ring system of ATX. Herein are reported our preliminary results leading to the successful synthesis of the F-I ring system of ATX and YTX.

To carry out the strategy outlined above, both the EF and the IJ ring systems required modification. From the previously described intermediate **3.92**, bis-homologation of the alkene followed by removal of the PMB group afforded the desired EF ring alcohol coupling precursor **3.112** (Figure 3.24).

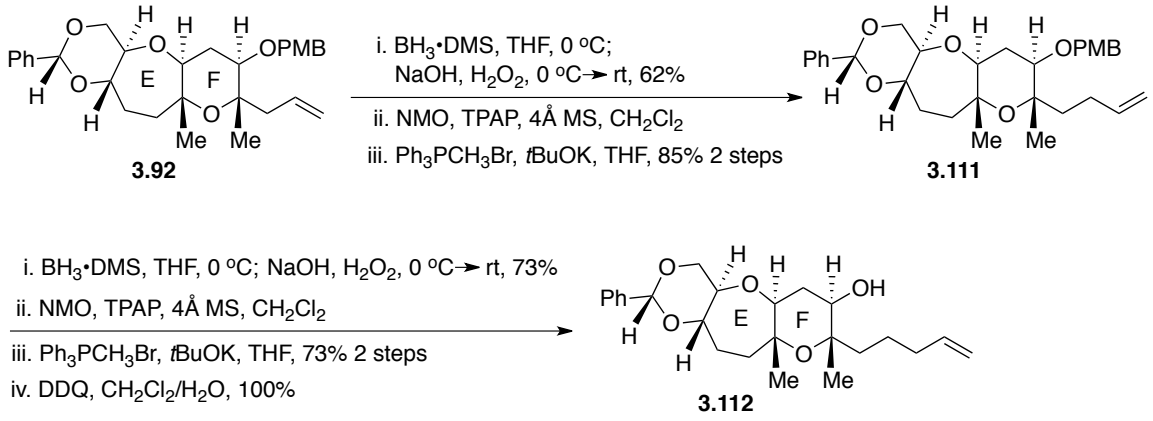


Figure 3.24. Synthesis of the EF ring coupling partner **3.112**

The previously described IJ ring precursor **3.49** was converted into the acid coupling partner **3.119** (Figure 3.25). The secondary alcohol was first protected as a TBS ether, and the acetate group on C36 was converted into a benzyl ether. Selective removal of the silylene group was achieved using HF•Py to give diol **3.114**. Conversion of the primary alcohol in **3.114** into a triflate and subsequent secondary TES ether formation afforded **3.115**. It is noteworthy that due to the steric environment at C31, the C31 hydroxy group in **3.114** could not be protected as a TBS ether. Treatment of **3.115** with lithium trimethylsilylacetylide successfully generated the desired terminal alkyne,

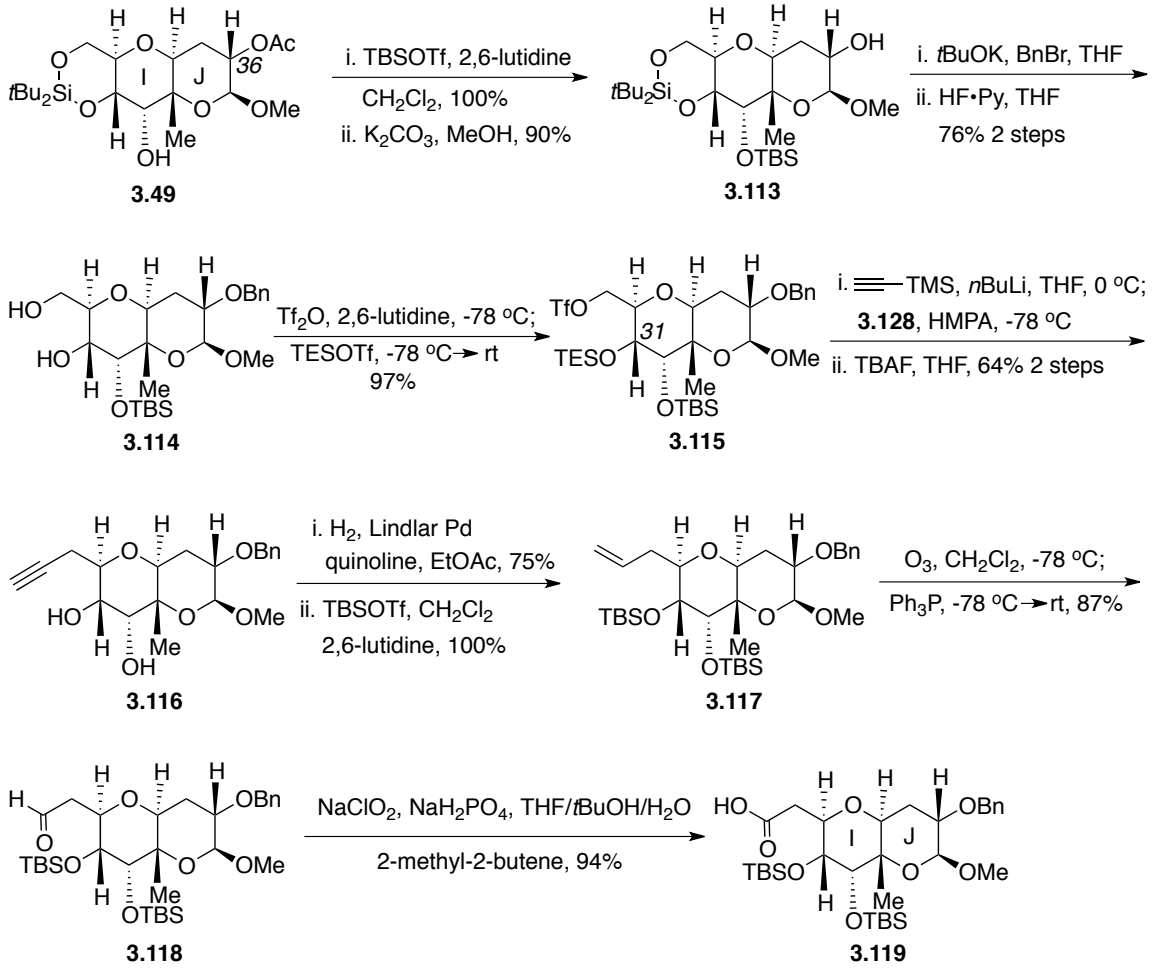


Figure 3.25. Synthesis of the IJ ring coupling partner **3.119**

however the TES ether on C31 underwent partial hydrolysis under reaction conditions. To facilitate the process, global silyl protecting group removal was accomplished using TBAF to afford diol **3.116**. Partial hydrogenation and reprotection of both alcohols as TBS ethers followed by ozonolysis and Pinnick oxidation gave the IJ ring acid coupling partner **3.119**.

The coupling of alcohol **3.112** and acid **3.119** was achieved using Yamaguchi's conditions (Figure 3.26). Disappointingly, when olefinic ester **3.120** was subjected to the modified Takai-Utimoto reaction conditions, only acyclic enol ether **3.121** was isolated in 65% yield. No desired cyclic enol ether product was observed. All efforts to convert the acyclic material **3.121** into the eight-membered G ring enol ether using ring-closing metathesis were futile due to problems associated with alkene isomerization.

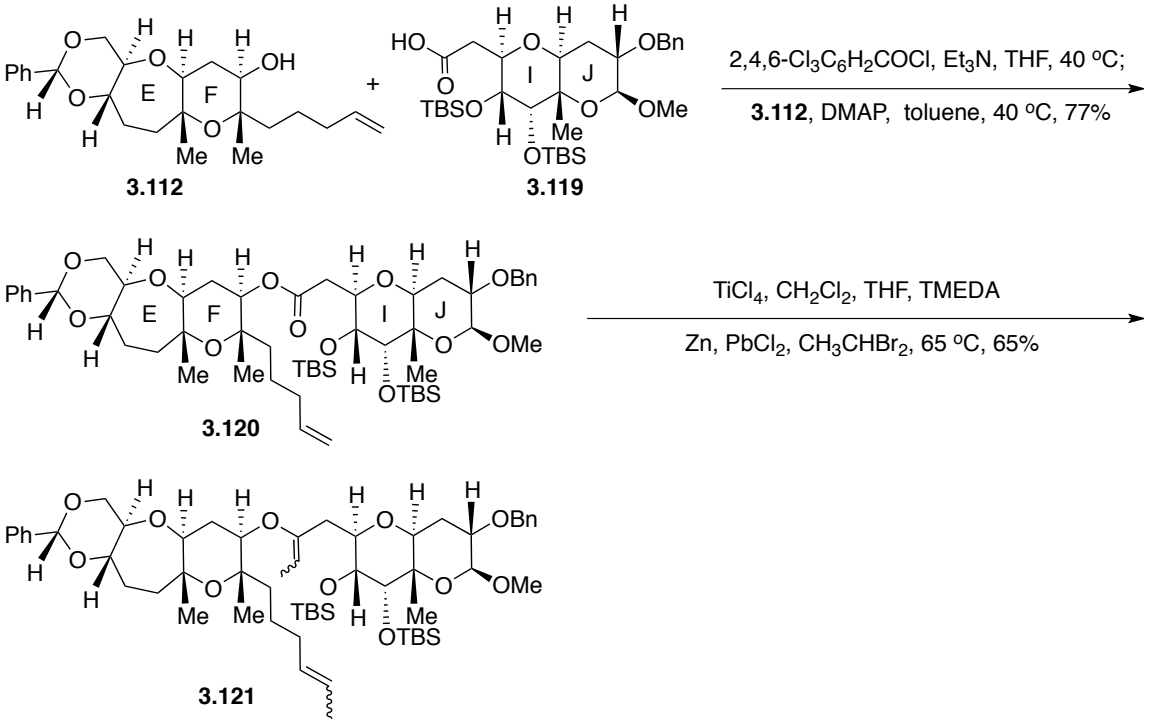


Figure 3.26. Efforts to synthesize the G ring from olefinic ester **3.120**

At that point, we suspected that the steric environment around the I ring in **3.119** due to the two TBS groups was prohibiting the formed terminal titanium alkylidene species from cyclizing onto the ester carbonyl. Moreover, we were concerned that the acetal group on the J ring might be too vulnerable for further manipulations. So we decided to employ an alternate I ring system **3.131** instead of **3.119** to further study the olefinic ester cyclization. The new I ring system would be less stereically congested and would have a side chain that we envisioned could be converted into the J ring at a later stage in the synthesis.

Using a similar strategy for synthesizing **3.119**, the synthesis of **3.131** is shown in Figure 3.27. From known compound **3.122**,[46] the secondary alcohol was converted into a tertiary alcohol through oxidation and methyl addition, which was followed by deprotection of the PMB group and oxidation to give hydroxy ketone **3.124**. After protection of the tertiary alcohol as a TMS ether, reduction of the ketone with L-selectride afforded alcohol **3.125**. Hydroboration of the alkene and oxidative work-up concomitantly removed the TMS group to give triol **3.126**. Tris-benzyl ether formation and removal of the silylene group generated diol **3.127.** One-pot primary triflate and secondary TES ether formation was followed by acetylide substitution and subsequent treatment with TBAF to afford hydroxy alkyne **3.129**. Reprotection of the alcohol as a TES ether and partial hydrogenation of the alkyne followed by ozonolysis and Pinnick oxidation generated the I ring system **3.131**.

Prior to examining the eight-membered cyclic enol ether formation with the new I ring system, we felt that the previous EF ring coupling precursor **3.112**, which was obtained in 23 steps from D-mannitol, was too valuable for our model study. As a result,

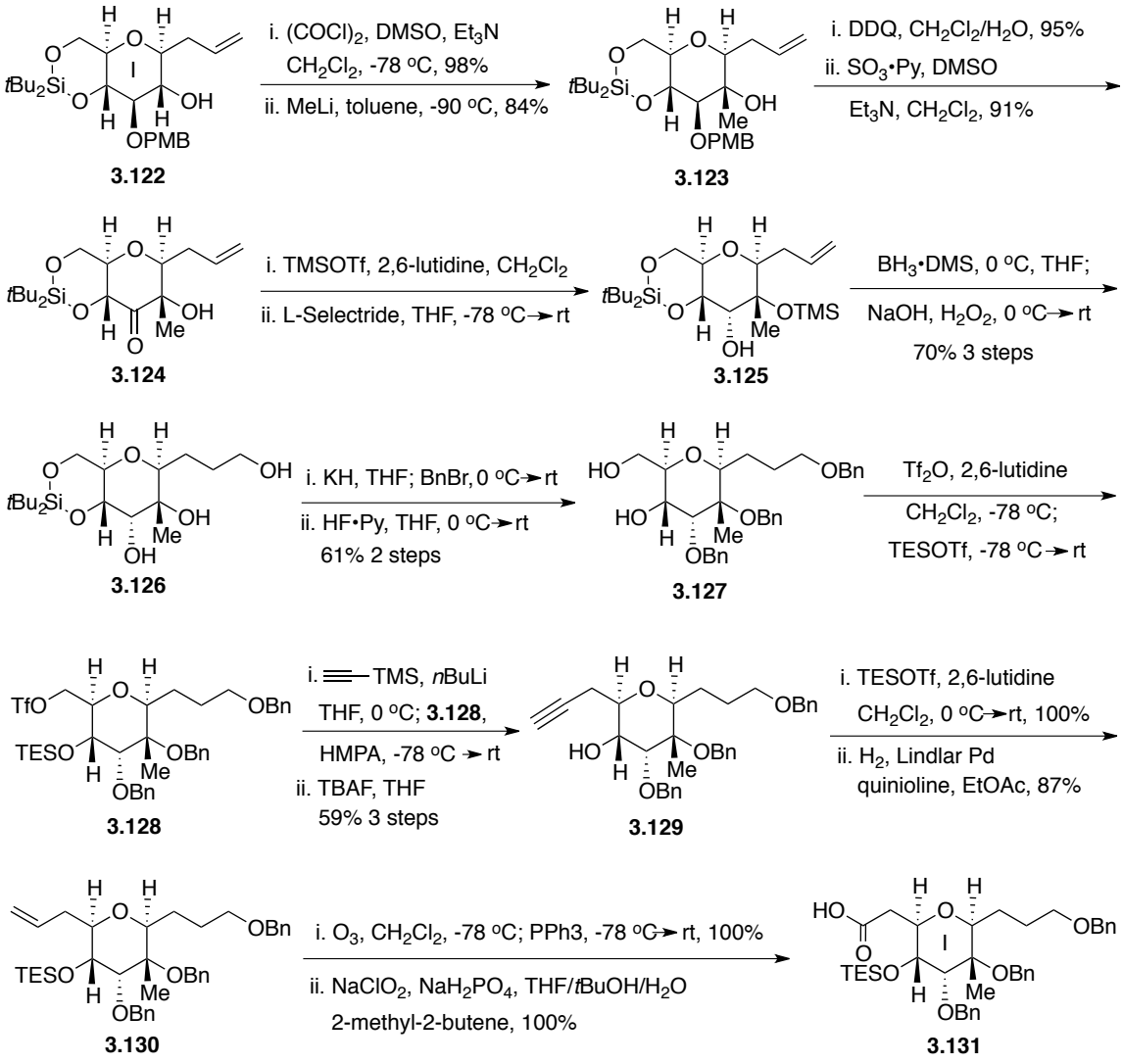


Figure 3.27. Synthesis of the I ring coupling partner **3.131**

a simpler compound **3.142** that consisted of the F ring of ATX was synthesized and employed (Figure 3.28). The left side of **3.142** was properly functionalized so that the E ring could be generated at a later stage.

From the previous intermediate **3.55**, acetylation led to the formation of **3.132**, which upon treatment with the reduced titanium ethylidene reagent afforded the F ring of ATX as enol ether **3.133**. Using the Claisen rearrangement strategy, ketone **3.136** was

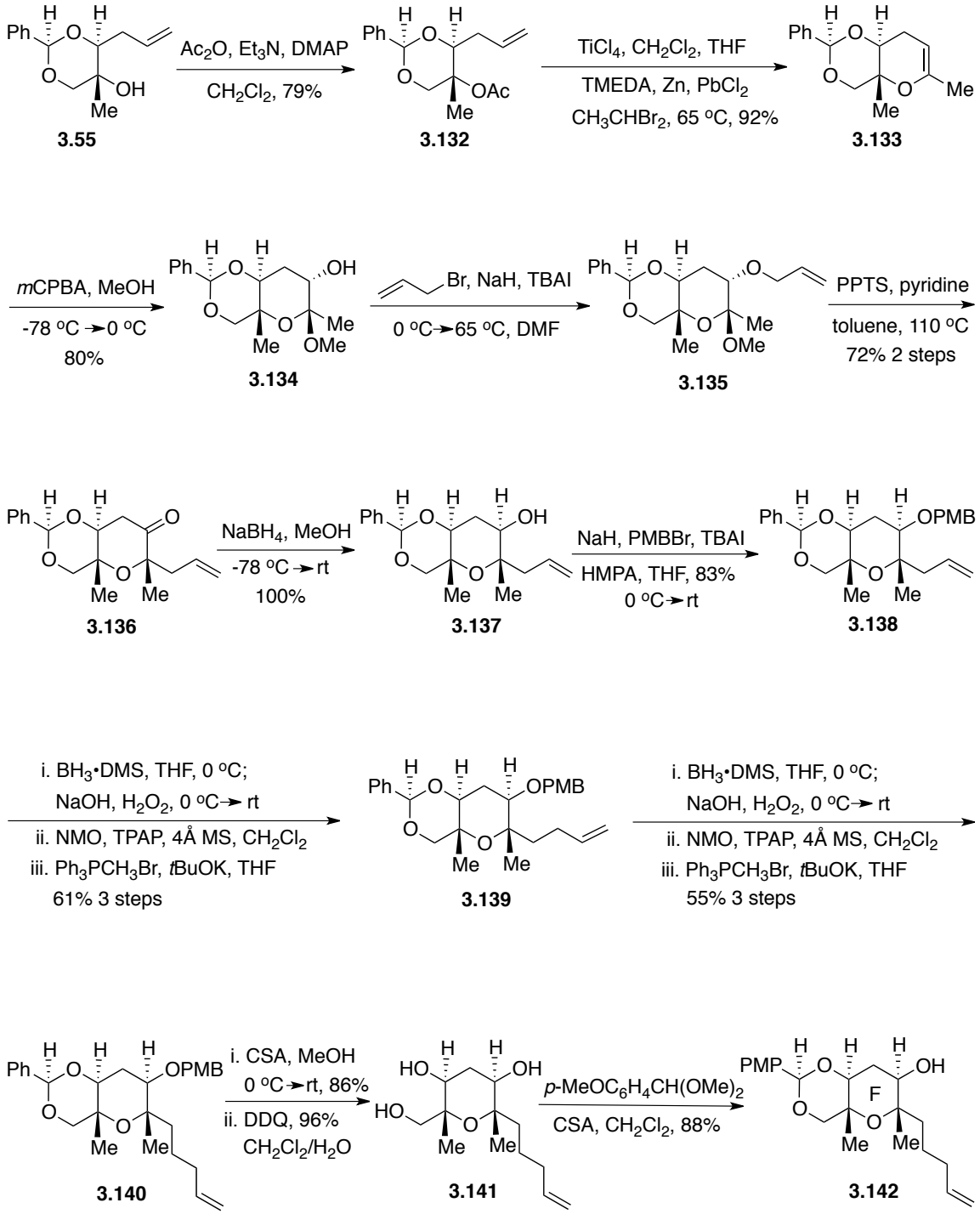


Figure 3.28. Synthesis of the F ring coupling partner **3.142**

obtained from **3.133** in three steps as a single stereoisomer. Reduction of the ketone and subsequent protection of the resulting alcohol as PMB ether afforded alkene **3.138**. Bis-homologation of the alkene gave **3.140**. At this point, we converted the benzylidene protecting group into its *p*-methoxy benzylidene analogue. The benzylidene acetal in **3.140** was removed using CSA in methanol. Subsequent removal of the PMB group afforded triol **3.141**, which was reprotected using anisaldehyde dimethylacetal and CSA to give the F ring alcohol coupling partner **3.142**.

With both the new acid and alcohol coupling partners **3.131** and **3.142**, we attempted again the eight-membered cyclic enol ether formation using olefinic ester cyclization (Figure 3.29). Yamaguchi esterification proceeded smoothly to give olefinic ester **3.143**. When **3.143** was subjected to the modified Takai-Utimoto conditions, to our great pleasure, the desired eight-membered cyclic enol ether **3.144** was generated in 40% yield along with 56% of the corresponding acyclic enol ether **3.145**. This result was in sharp contrast with our previous results shown in Figure 3.26, where no cyclic enol ether was obtained.

Pleased as we were, we were very curious about the reason behind these vastly different results. Since the right side of the F ring systems in both **3.112** and **3.142** where the cyclizations took place were identical, it seemed that the steric environment difference on the I rings in **3.119** and **3.131** was the cause of the different cyclization outcome. To test this argument, a control experiment was performed using the new I ring acid coupling partner **3.131** and the previous EF ring alcohol coupling partner **3.112** (Table 3.1, entry 1). Interestingly, under the same reaction conditions, the eight-membered cyclic enol ether product was obtained in 22% yield together with 55% of the

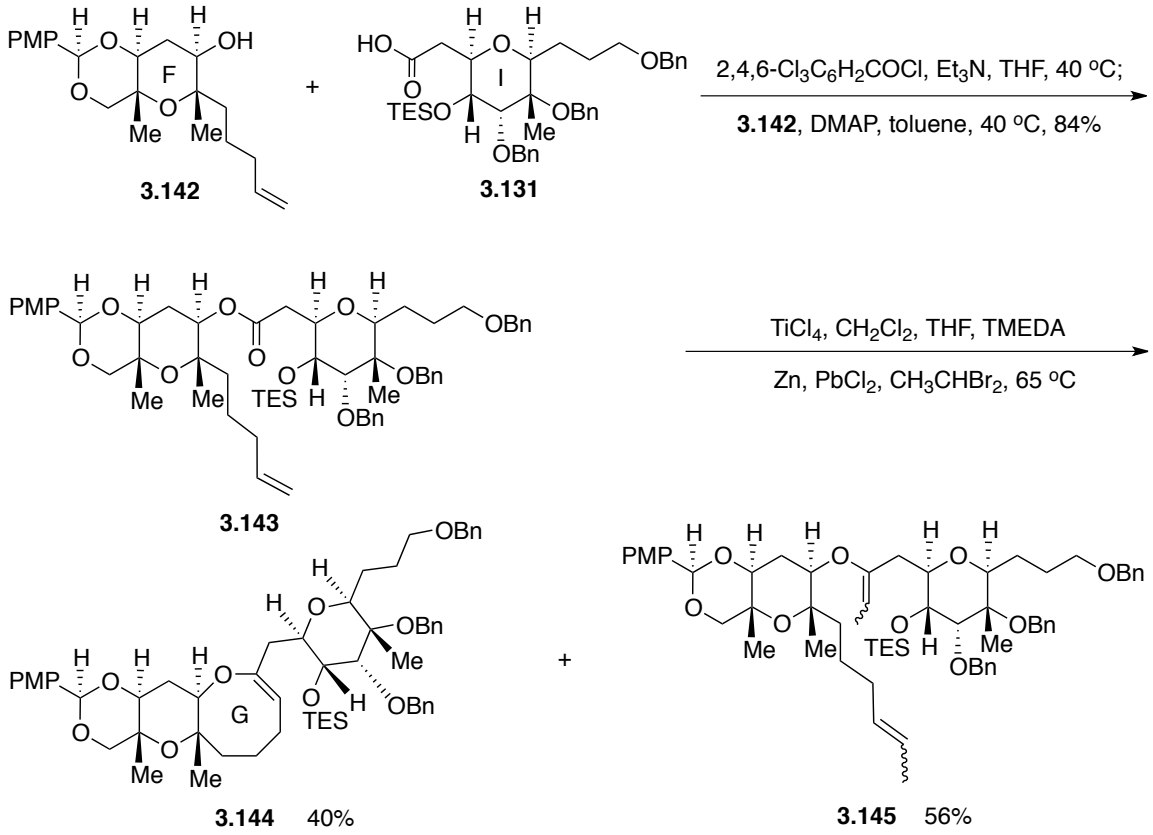
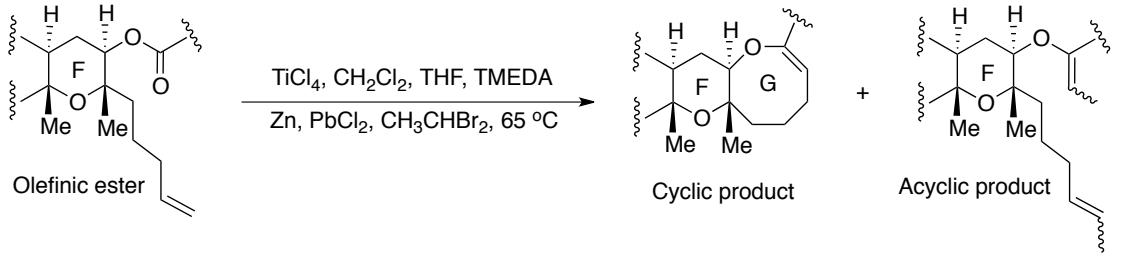


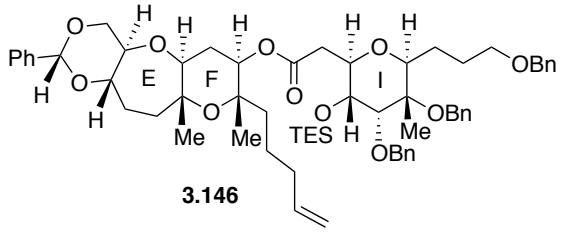
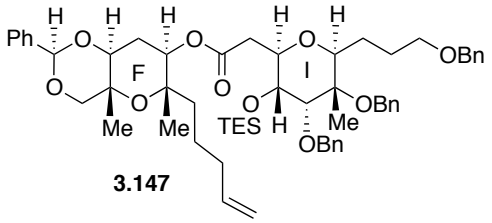
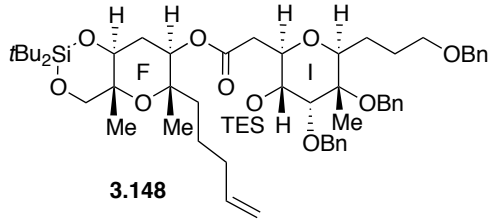
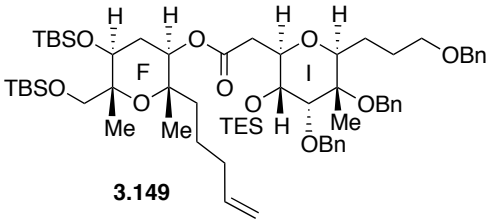
Figure 3.29. Synthesis of the G ring of ATX

acyclic product from olefinic ester **3.146**. This result implied that the steric environment on the I ring did play an important role in this particular cyclization. However, the lower yield of the cyclic product in this reaction comparing to the one shown in Figure 3.29 (22% vs 40%) also suggested the F ring system **3.142** had a higher tendency to cyclize under the reaction conditions than the previous EF ring system **3.112**.

Intrigued by the different reactivity outlined above, we also examined substrates having different protecting groups on the F ring (Table 3.1, entry 2-4). To our disappointment, no significant increase in yield of the eight-membered cyclic enol ether products was observed.

Table 3.1. Studies on formation of G ring using olefinic ester cyclization



Entry	Olefinic ester	Cyclic product	Acyclic product
1	 **3.146**	22%	55%
2	 **3.147**	38%	52%
3	 **3.148**	40%	56%
4	 **3.149**	42%	51%

Although the 40% yield was not ideal, we decided to carry the obtained eight-membered G ring enol ether **3.144** on to explore the formation of the six-membered H ring (Figure 3.30). Starting from the G ring enol ether **3.144**, oxidation with DMDO and in situ reduction of the resulting epoxide with *i*Bu_2AlH afforded the corresponding secondary alcohol. Oxidation using Ley's conditions gave ketone **3.150** as a single stereoisomer. We believe the stereoselectivity in the DMDO oxidation comes from the presence of the C23 methyl group. Borrowing from Oishi's synthesis of the A-J ring system of YTX, a kinetically controlled methylation with LiHMDS and MeI stereoselectively installed the C26 methyl group to give **3.151**.[23a] Having the requisite

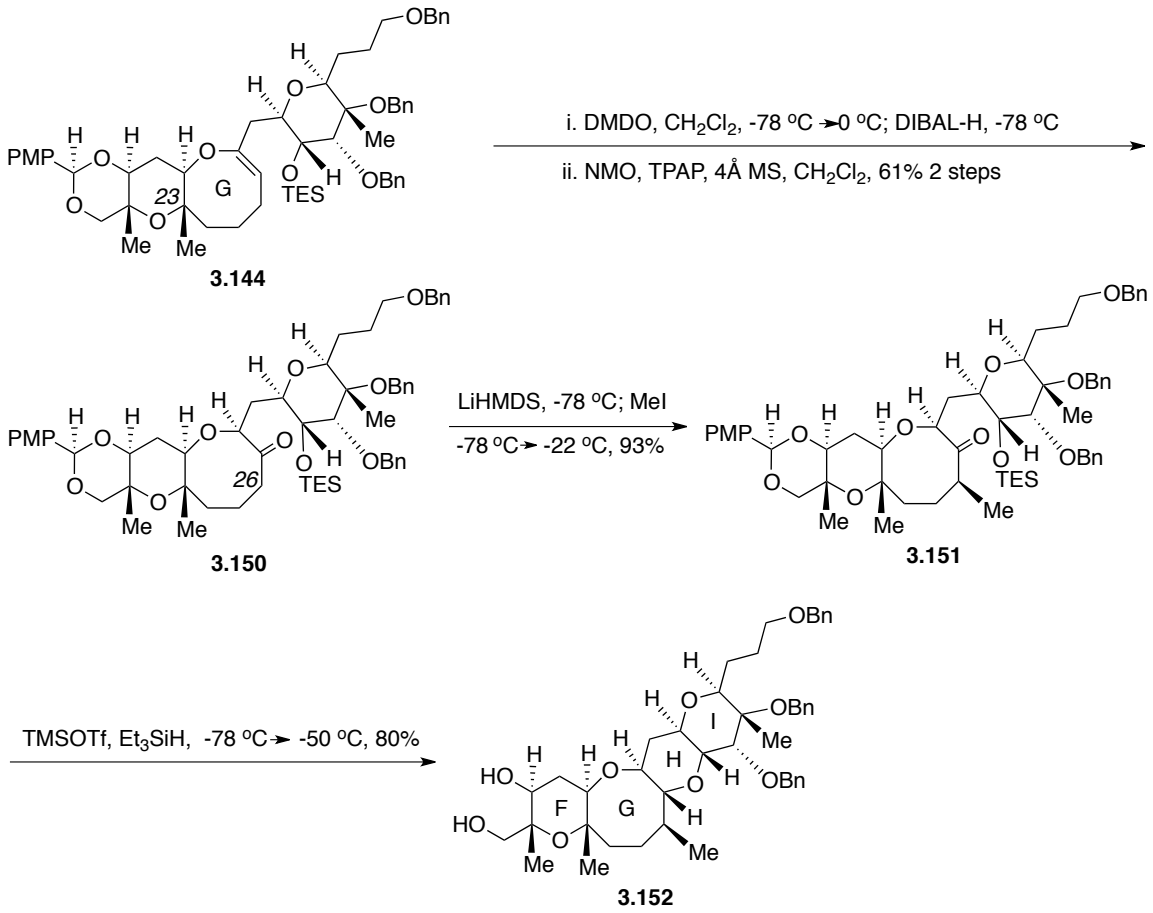


Figure 3.30. Synthesis of the F-I ring system of ATX

functionality in place, we planned to employ an *O,S*-mixed ketal radical reduction to form the H ring as in our synthesis of the A-F ring system of ATX. Surprisingly however, neither HF•Py nor TBAF led to a clean removal of the TES group. Finally, a direct reductive cyclization of the TES-protected hydroxy ketone **3.151** using TMSOTf and Et_3SiH successfully afforded the desired H ring with concomitant removal of the *p*-methoxy benzylidene group to give diol **3.152**.[24e] When a benzylidene group rather than a *p*-methoxy benzylidene was used on the F ring, it could not be cleanly removed under the reductive cyclization conditions, giving instead a mixture of benzyl protected alcohols. The formation of diol **3.152** represented a synthesis of the F-I ring system of ATX, and since the A-I ring structure of ATX is identical to YTX, it also represents a synthesis of the F-I ring system of YTX.

To summarize, we have successfully synthesized the F-I ring system of ATX and YTX using a highly convergent strategy that employs an olefinic ester cyclization to form the eight-membered G ring. Although further studies on the formation of eight-membered cyclic enol ethers using olefinic ester cyclization are certainly needed, the synthesis process has provided us with useful information about the substrate scope of this methodology. Other highlights in this synthesis include a stereoselective installment of the C26 methyl group under substrate control and a highly efficient reductive cyclization to form the H ring.

The future plan for the synthesis of the A-I ring system of ATX is shown in Figure 3.31. We envision that the E ring can be formed from the F-I ring diol **3.152** in three steps, and that the E-I ring coupling partner **3.154** will be generated using our *C*-glycoside forming chemistry. Coupling the AB ring system **3.91** and the E-I ring system

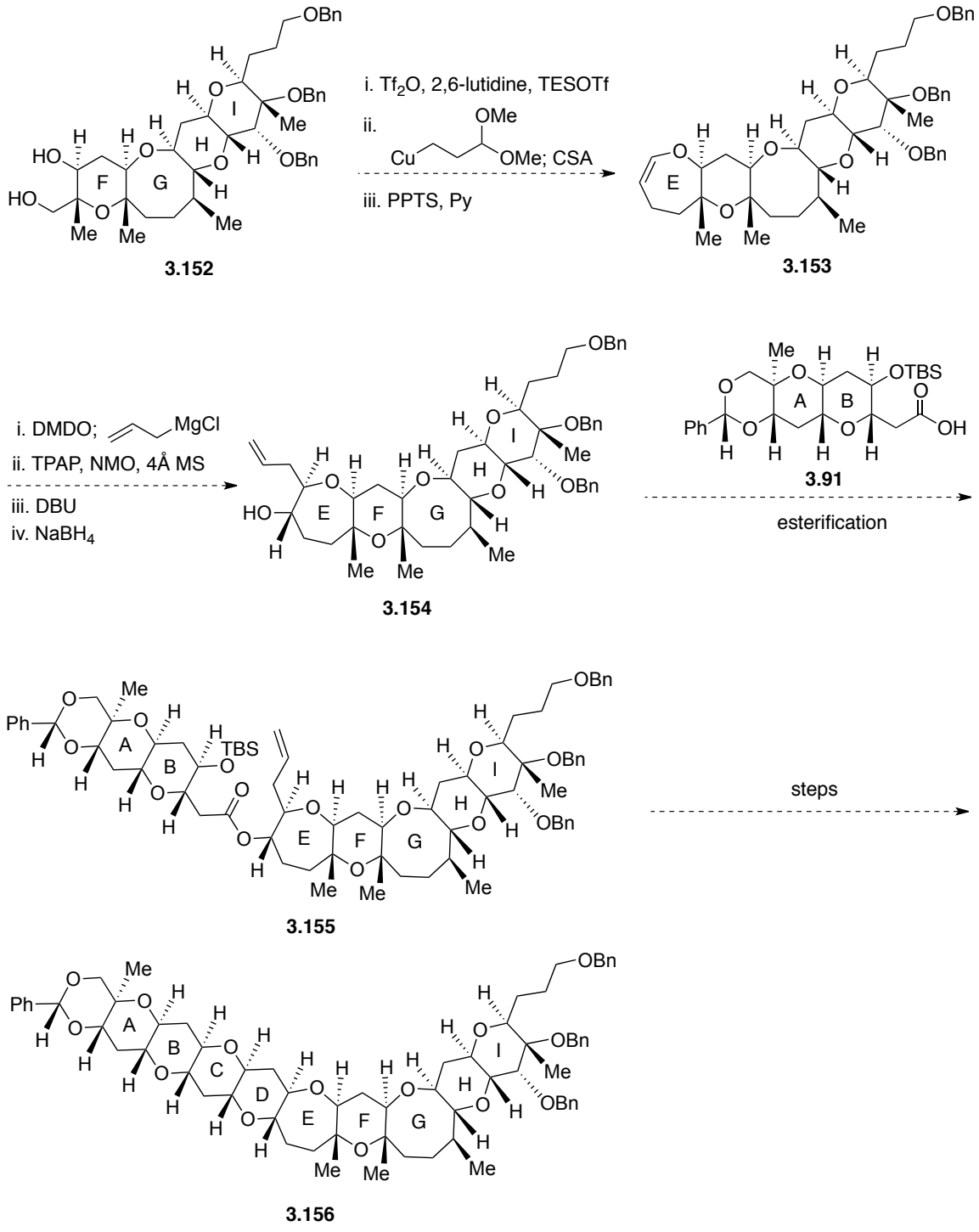


Figure 3.31. Future plan for construction of the A-I ring system of ATX

3.154 through esterification will give ester **3.155**, which will be converted to the A-I ring system **3.156** using the same reaction sequence as in our synthesis of the A-F ring system.

The future plan to complete the total synthesis of ATX is shown in Figure 3.32. One carbon elongation on C2 and protecting group manipulation will give **3.157**, which will be subsequently converted to C37 acetal **3.158**.[47] Removal of the benzyl groups and acid-promoted cyclization will give the J ring as enol ether **3.159**. Functionalization of the J ring, deprotection, and sulfate formation will furnish ATX (**3.2**).

Conclusion

In this chapter, we have described our syntheses of the A-F ring system and the F-I ring system of ATX and YTX. Both syntheses employed a highly convergent coupling strategy, which relies on esterification to unify two subunits and subsequent olefinic ester cyclization. In addition, our iterative cyclic enol ether/*C*-glycoside formation sequence was extensively used in the synthesis of all three bicyclic coupling subunits. All the new stereocenters in the synthesis were generated using substrate control with the orginal stereocenters coming from the chiral pool.

Experimentals

NMR spectra were recorded on Varian Inova-400 MHz, Varian Inova-500 MHz or Varian VXR-500 MHz spectrometers. Chemical shifts were reported in δ, parts per million (ppm), relative to benzene (7.16), chloroform (7.27), or dichloromethane (5.32) as internal standards. Coupling constants, *J*, were reported in Hertz (Hz) and refer to

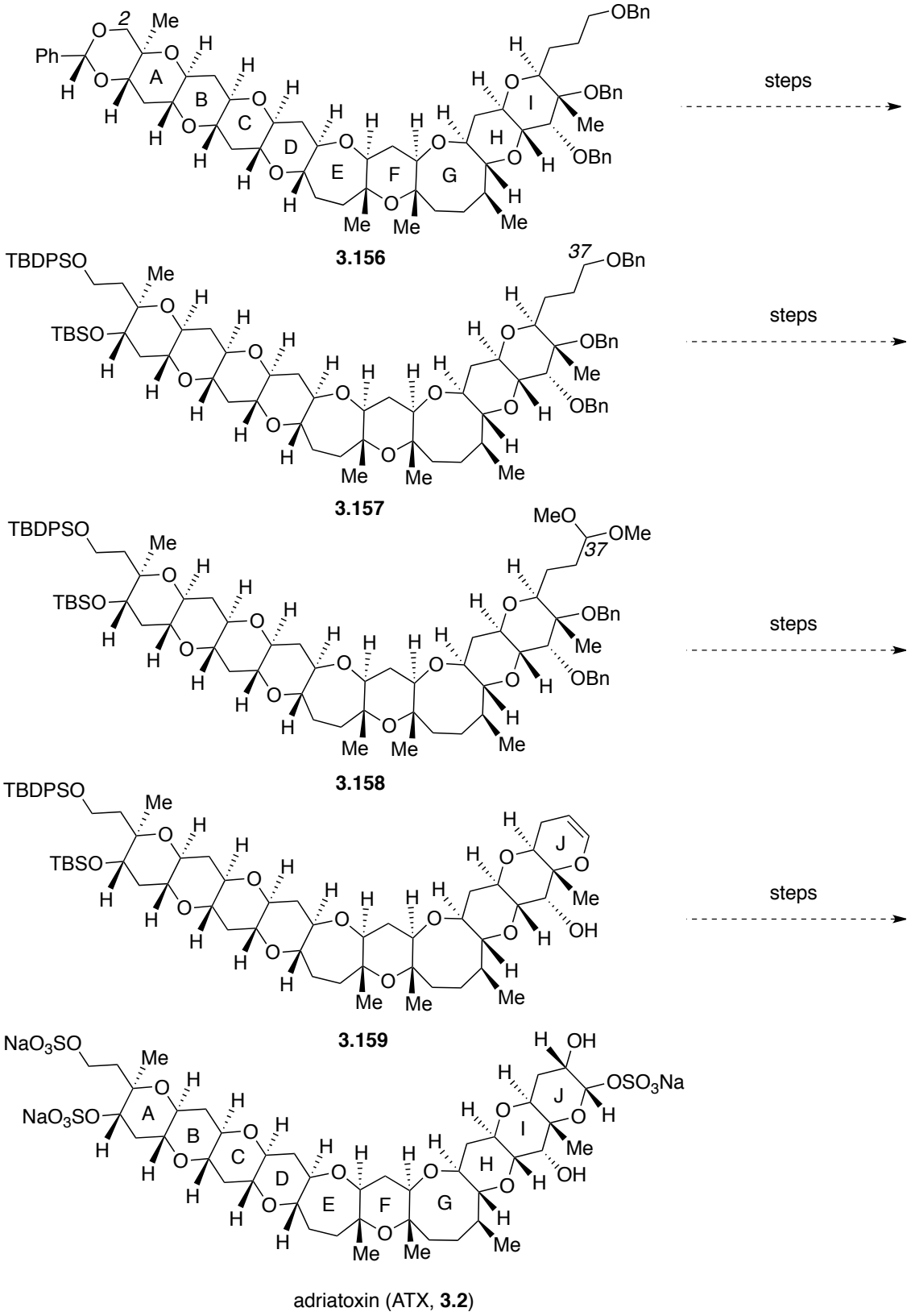
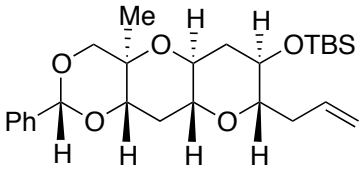


Figure 3.32. Future plan to complete the total synthesis of ATX

apparent peak multiplicities and not true coupling constants. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass spectrometer. IR spectra wererecorded on a Bruker Tensor 27 FT-IR spectrometer. Optical rotations were obtained on a Perkin-Elmer Model 343 polarimerter (Na D line) using a microcell with 1 dm path length. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin: Oxford, 1966). Dichloromethane, 2,6-lutidine, triethylamine, TMEDA, chlorobenzene and pyridine were distilled from CaH_2. Tetrahydrofuran and diethyl ether were dried from the sodium ketyl of benzophenone and distilled before use. Zinc dust (<10 μm, Aldrich) was activated by washing with 5% hydrochloric acid, H_2O, methanol, and ether and dried in vacuo overnight. All other reagents were used without further purification. Unless otherwise noted, all reactions were performed under a nitrogen atmosphere in flame-dried glassware using standard syringe, cannula, and septa apparatus. Concentration refers to removal of solvent under reduced pressure (house vacuum at ca. 20mm Hg). Analytical thin–layer chromatography (TLC) was performed on silica gel plates (0.25 mm) precoated with a fluorescent indicator. Flash chromatography was performed using 40–63 μm silica gel (200 X 400 mesh).

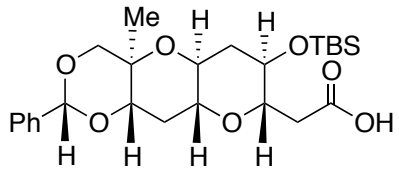
Procedures and Characterizations

The characterization and procedures for compounds **3.47**, **3.48**, **3.55**, and **3.82** were previously published.[31c]



3.89

Preparation of TBS ether 3.89. To a solution of **3.47** (25 mg, 0.072 mmol) and 2,6-lutidine (25 μL, 0.22 mmol) in CH_2Cl_2 (10 mL) was added TBSOTf (25 μL, 0.11 mmol). The reaction mixture was stirred for 2 h and quenched with sat. $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (8:1 hexanes: ethyl acetate) provided 30 mg of **3.89** (90%) as a colorless oil. R_f 0.60 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -48.9° (c = 0.47, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.60 (d, *J* = 7.3 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.13 (t, *J* = 7.3 Hz, 1H), 6.14 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1H), 5.40 (s, 1H), 5.22 (bd, *J* = 17.1 Hz, 1H), 5.13 (bd, *J* = 10.2 Hz, 1H), 3.92 (d, *J* = 10.0 Hz, 1H), 3.53 (d, *J* = 10.0 Hz, 1H), 3.47 (ddd, *J* = 10.7, 7.3, 4.9 Hz, 1H), 3.38 (ddd, *J* = 10.2, 9.3, 3.4 Hz, 1H), 3.35 (dd, *J* = 12.5, 3.5 Hz, 1H), 3.26 (ddd, *J* = 8.8, 8.8, 2.9 Hz, 1H), 2.94 (ddd, *J* = 10.2, 9.8, 4.9 Hz, 1H), 2.75-2.69 (m, 1H), 2.35 (ddd, *J* = 7.3, 7.3, 7.3 Hz, 1H), 2.31 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 2.19 (ddd, *J* = 11.2, 4.4, 4.4 Hz, 1H), 1.88 (ddd, *J* = 11.2, 11.2, 11.2 Hz, 1H), 1.43 (s, 3H), 0.93 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 138.5, 135.3, 128.8, 128.2, 126.7, 116.8, 102.8, 82.6, 79.9, 78.2, 76.4, 70.3, 69.9, 69.6, 40.1, 36.4, 30.9, 25.8, 18.0, 15.2, -4.0, -4.8; IR (neat) 2955, 2933, 2859, 1463, 1380, 1331, 1254, 1092 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{26}H_{41}O_5Si$ 461.3 ($M+H^+$), found 461.3.

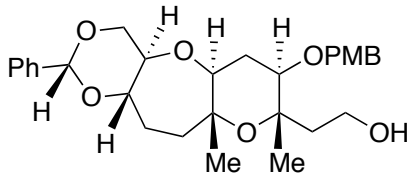


3.91

Preparation of acid 3.91. To a solution of **3.89** (30 mg, 0.065 mmol) in CH_2Cl_2 (20 mL) at -78 ^oC was bubbled through O_3 until the reaction developed a light blue color. The excess O_3 was purged from the reaction mixture by bubbling N_2 through it until the light blue color completely faded away. Triphenylphosphine (51 mg, 0.19 mmol) was then added and the mixture was allowed to slowly warm up to rt. After 12 h, the solution was concentrated under reduced pressure. Flash chromatography (50:1 to 5:1 hexanes:ethyl acetate) provided aldehyde **3.90** (28 mg, 92%) as a colorless oil.

To a solution of **3.90** (28 mg, 0.061 mmol) in THF (3 mL) was successively added *t*BuOH (3 mL), H_2O (3mL), 2-Me-2-butene (0.6 mL), NaH_2PO_4 (36 mg, 0.30 mmol) and $NaClO_2$ (27 mg, 0.30 mmol). The reaction mixture was stirred at rt for 2 h and H_2O (3mL) was added in. The reaction mixture was extracted with ethyl acetate (3 x 5 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate to ethyl acetate) provided acid **3.91** (19 mg, 67%) as a colorless oil. R_f 0.30 (2:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -52.2° (c = 0.39, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.51-7.47 (m, 2H), 7.41-7.37 (m, 3H), 5.58 (s, 1H), 3.92 (d, *J* = 10.2 Hz, 1H), 3.69-3.60 (m, 3H), 3.55 (ddd, *J* = 10.7, 9.3, 4.9 Hz, 1H), 3.48 (ddd, *J* = 11.2, 9.3, 3.9 Hz, 1H), 3.22 (ddd, *J* = 11.2, 9.8, 4.4 Hz, 1H), 2.89 (dd, *J* = 15.6, 2.9 Hz, 1H), 2.42 (dd, *J* = 15.6, 9.3 Hz, 1H), 2.27 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 2.20 (ddd, *J* = 11.2, 4.4, 4.4 Hz, 1H), 1.78 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.53 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.52 (s, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C

NMR (125 MHz, CD_2Cl_2) δ 177.2, 138.1, 129.2, 128.4, 126.5, 103.1, 79.8, 79.6, 78.2, 76.4, 70.3, 70.0, 69.3, 39.5, 37.7, 30.6, 25.7, 17.9, 15.1, -4.1, -4.9; IR (neat) 3259, 2954, 2861, 1714, 1463, 1377, 1256, 1093 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{25}H_{37}O_7Si$ 477.3 ($M-H^+$), found 477.4.

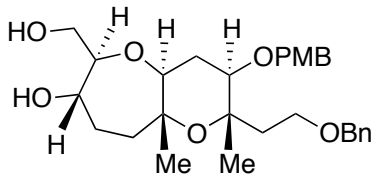


3.93

Preparation of alcohol 3.93. To a solution of **3.48** (28 mg, 0.075 mmol) in THF (5 mL) was added KH (30 mg 30% dispersion in mineral oil, 0.23 mmol). The reaction mixture was stirred for 10 min at rt and then DMPU (4.5 μL, 0.038 mmol), PMBBr (54 μL, 0.38 mmol) and catalytic amount of TBAI were added. The reaction mixture was stirred for overnight at rt before it was quenched with sat. NH_4Cl (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) gave a colorless oil which was brought to the next step without further purification.

To a solution of the PMB ether obtained from the last step in CH_2Cl_2 (20 mL) at -78 ^oC was bubbled through O_3 until the reaction developed a light blue color. The excess O_3 was purged from the reaction mixture by bubbling N_2 through it for 10 min until the light blue color completely faded away. Triphenylphosphine (59 mg, 0.23 mmol) was then added and the mixture was allowed to slowly warmed up to rt. After 12 h, the solution was concentrated under reduced pressure. Flash chromatography (50:1 to 5:1 hexanes:ethyl acetate) provided aldehyde as a colorless oil.

To a solution of the aldehyde obtained from the last step in MeOH (5 mL) at 0 °C was added $NaBH_4$ (8.5 mg, 0.23 mmol). The reaction mixture was quenched with acetone (3 mL) after stirring for 2 h at 0 °C. The solvent was then removed under reduced pressure and the residue was purified using flash chromatography (4:1 hexanes:ethyl acetate) to give **3.93** as a colorless oil (28 mg, 74% 3 steps). R_f 0.50 (2:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -15.5° (c = 0.45, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.54-7.51 (m, 2H), 7.44-7.38 (m, 3H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 5.45 (s, 1H), 4.64 (d, *J* = 11.2 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.33 (dd, *J* = 10.2, 4.9 Hz, 1H), 3.83 (s, 3H), 3.84-3.78 (partially obscured m, 1H), 3.61 (dd, *J* = 10.3, 10.3 Hz, 1H), 3.54 (ddd, *J* = 9.8, 9.8, 4.9 Hz, 1H), 3.50 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.37 (dd, *J* = 12.2, 3.4 Hz, 1H), 3.15 (br s, 1H), 2.30-2.17 (m, 2H), 1.96-1.85 (m, 4H), 1.79 (ddd, *J* = 12.2, 12.2, 12.2 Hz, 1H), 1.74 (ddd, *J* = 14.7, 7.8, 3.9 Hz, 1H), 1.34 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.6, 138.3, 130.7, 129.5, 129.1, 128.4, 126.4, 113.9, 100.9, 83.2, 80.4, 79.2, 78.9, 78.1, 74.8, 70.8, 69.7, 59.3, 55.5, 43.5, 39.5, 28.7, 28.5, 21.9, 21.0; IR (neat) 3448, 2946, 2870, 1613, 1513, 1458, 1377, 1248, 1096 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{29}H_{38}O_7Na$ 521.2 ($M+Na^+$), found 521.3.

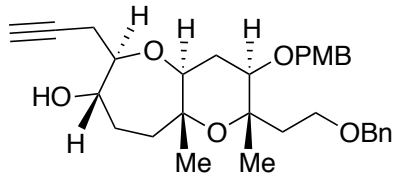


3.94

Preparation of diol 3.94. To a solution of **3.93** (0.126 g, 0.253 mmol) in THF (5 mL) at rt was added *t*BuOK (0.50 mL of 1.0 M solution in THF, 0.50 mmol). The mixture was stirred for 30 min before it was cooled to 0 °C. Then BnBr (0.12 mL, 1.01 mmol) was added slowly and the reaction mixture was stirred for 3 h before it was

quenched with sat. NH_4Cl (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated.

The residue from above was dissolved in MeOH (15 mL) and the mixture was cooled to 0 ^oC. CSA (15 mg, 0.065 mmol) was added and the reaction mixture was allowed to slowly warm up to rt. After 5 h, the reaction mixture was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate) gave **3.94** as a colorless oil (0.112 g, 89% 2 steps). R_f 0.60 (ethyl acetate); $[\alpha]^{20}_D$ = -19.0° (c = 0.51, THF); ^1H NMR (500 MHz, CD_2Cl_2) δ 7.40-7.30 (m, 5H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.59 (d, *J* = 11.2 Hz, 1H), 4.48 (s, 2H), 4.38 (d, *J* =10.7 Hz, 1H), 3.87 (br d, *J* = 5.5 Hz, 1H), 3.82 (s, 3H), 3.71 (br s, 1H), 3.64-3.60 (m, 2H), 3.55-3.48 (m, 3H), 3.44 (dd, *J* = 11.2, 4.2 Hz, 1H), 2.70 (br s, 2H), 2.17 (ddd, *J* = 11.7, 3.9, 3.9 Hz, 1H), 1.95-1.76 (m, 4H), 1.76-1.65 (m, 2H), 1.54 (ddd, *J* = 13.7, 6.3, 2.2 Hz, 1H), 1.27 (s, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.4, 139.2, 131.1, 129.4, 128.5, 127.9, 127.6, 113.9, 85.7, 79.6, 79.3, 76.5, 75.5, 73.0, 71.7, 70.8, 66.7, 64.5, 55.4, 41.7, 36.2, 28.8, 27.9, 22.3, 20.2; IR (neat) 3383, 2929, 2870, 1613, 1455, 1375, 1248, 1090 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{29}H_{40}O_7Na$ 523.3 ($M+Na^+$), found 523.3.



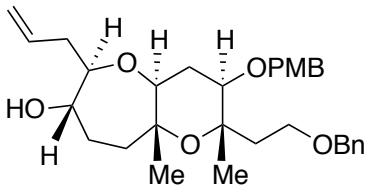
3.97

Preparation of alkyne 3.97. To a solution of **3.94** (0.112 g, 0.224 mmol) and 2,6-lutidine (0.104 mL, 0.893 mmol) in CH_2Cl_2 (20 mL) at -78 ^oC was added

trifluoromethanesulfonic anhydride (40.0 μL, 0.234 mmol). The reaction mixture was stirred for 30 min at -78 ^{o}C and TBSOTf (77.0 μL, 0.335 mmol) was added. The reaction mixture was then slowly warmed to rt before it was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated to give a yellow oil. The oil was quickly passed through a plug of silica gel (10:1 hexanes:ethyl acetate) and concentrated. The resulting colorless oil **3.95** was used directly in the next step without additional purification.

To a solution of trimethylsilylacetylene (0.168 mL, 1.19 mmol) in THF (10 mL) at 0 ^{o}C was added *n*BuLi (0.474 mL of 2.5 M solution in hexanes, 1.19 mmol). The reaction mixture was stirred at 0 ^{o}C for 30 min and then cooled to -78^{o}C. A solution of **3.95** obtained from above and HMPA (0.207 mL, 1.19 mmol) in THF (5 mL) was cannulated into the reaction mixture. The reaction mixture was stirred at -78^{o}C for 2 hours before it was quenched with sat. NH_4Cl (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated to give a dark brown syrup which was taken up in THF (10 mL). To the solution was added TBAF (1.12 mL of 1.0 M solution in THF, 1.12 mmol) and the mixture was stirred at rt overnight before it was quenched with sat. NH_4Cl (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes:ethyl acetate) gave **3.97** as a colorless oil (85.7 mg, 75% 3 steps). R_f 0.50 (2:1 hexanes:ethyl acetate); $[\alpha]^{20}_{D}$ = -21.6° (c = 0.42, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.40-7.28 (m, 5H), 7.27 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.3 Hz, 2H), 4.58 (d, J = 10.8 Hz, 1H), 4.48 (s, 2H), 4.38

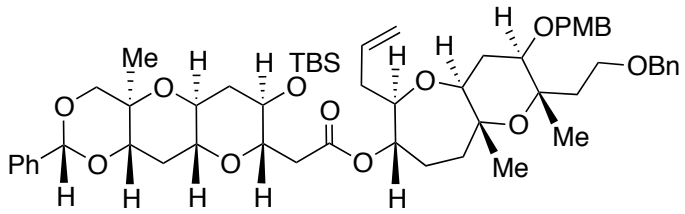
(d, *J* =11.2 Hz, 1H), 4.08 (br s, 1H), 3.81 (s, 3H), 3.79 (partially obscured ddd, *J* = 7.3, 5.4, 1.5 Hz, 1H), 3.63-3.59 (m, 2H), 3.52 (dd, *J* = 12.2, 4.2 Hz, 1H), 3.42 (dd, *J* = 11.7, 3.9 Hz, 1H), 3.41 (ddd, *J* = 16.6, 5.4, 2.4 Hz, 1H), 2.33 (ddd, *J* = 17.1, 7.8, 2.7 Hz, 1H), 2.18-2.10 (partially obscured m, 1H), 2.13 (ddd, *J* = 12.2, 3.9, 3.9 Hz, 1H), 2.10 (t, *J* = 2.4 Hz, 1H), 1.94-1.75 (m, 5H), 1.68 (ddd, *J* = 12.2, 12.2, 12.2 Hz, 1H), 1.51 (ddd, *J* = 13.2, 5.9, 2.9 Hz, 1H), 1.25 (s, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.4, 139.3, 131.2, 129.4, 128.5, 127.8, 127.6, 113.8, 83.3, 81.2, 79.5, 78.5, 76.5, 75.4, 73.3, 73.0, 70.8, 70.1, 66.7, 55.4, 41.7, 35.9, 28.7, 26.7, 24.6, 22.2, 20.1; IR (neat) 3419, 2929, 2869, 2339, 1613, 1454, 1374, 1248, 1089 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{31}H_{40}O_6Na$ 531.3 ($M+Na^+$), found 531.3.



3.98

Preparation of alkene 3.98. To a solution of **3.97** (85.7 mg, 0.169 mmol) in ethyl acetate (10 mL) was added quinoline (10 μL, 0.085 mmol) and Lindlar's Pd catalyst (10 mg). The mixture was stirred under H_2 atmosphere for 2 h before it was passed through a Celite plug with ethyl acetate. The filtrate was concentrated and flash chromatography (4:1 hexanes:ethyl acetate) gave **3.98** as a colorless oil (78.8 mg, 92%). R_f 0.55 (2:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -14.9° (c = 0.43, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.38-7.28 (m, 5H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 5.89 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.14-5.07 (m, 2H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.47 (s, 2H), 4.37 (d, *J* = 11.2 Hz, 1H), 3.89 (br d, *J* = 5.9 Hz, 1H), 3.80 (s, 3H), 3.68 (ddd, *J* = 6.4, 6.4, 1.4 Hz, 1H), 3.62-3.58 (m, 2H), 3.47 (dd, *J* = 12.2, 4.2 Hz, 1H), 3.41 (dd, *J* =

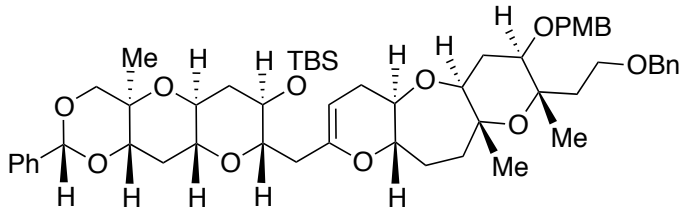
11.7, 3.9 Hz, 1H), 2.27-2.15 (m, 2H), 2.10 (ddd, *J* = 12.2, 4.4, 3.9 Hz, 1H), 1.93-1.80 (m, 4H), 1.78-1.69 (m, 2H), 1.65 (ddd, *J* = 12.2, 12.2, 12.2 Hz, 1H), 1.49 (ddd, *J* = 13.2, 5.3, 2.7 Hz, 1H), 1.24 (s, 6H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.4, 139.3, 135.4, 131.2, 129.4, 128.5, 127.8, 127.5, 116.9, 113.8, 84.7, 79.6, 78.5, 76.5, 75.4, 73.7, 72.9, 70.7, 66.7, 55.4, 41.7, 39.4, 35.9, 28.8, 26.7, 22.3, 20.1; IR (neat) 3423, 2929, 1613, 1513, 1454, 1374, 1248, 1087 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{31}H_{42}O_6Na$ 533.3 ($M+Na^+$), found 533.3.



3.99

Preparation of ester 3.99. To a solution of acid **3.91** (36.0 mg, 0.0753 mmol) in THF (8 mL) was added triethylamine (45.9 μL, 0.330 mmol) and 2,4,6-trichlorobenzoyl chloride (35.3 μL, 0.223 mmol). The reaction mixture was heated at 40 ^{o}C for 2 h before the solvent was removed in vacuo. To the resulting residue was cannulated a solution of alcohol **3.98** (36.8 mg, 0.0722 mmol) in toluene (10 mL). DMAP (42.3 mg, 0.347 mmol) was then added and the reaction mixture was heated at 40 ^{o}C for 2 h. The reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) provided ester **3.99** (67.8 mg, 97%) as a colorless oil. R_f 0.25 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -14.8° (c = 0.30, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.46-7.43 (m, 2H), 7.38-7.34 (m, 7H), 7.32-7.27 (m, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.8 Hz,

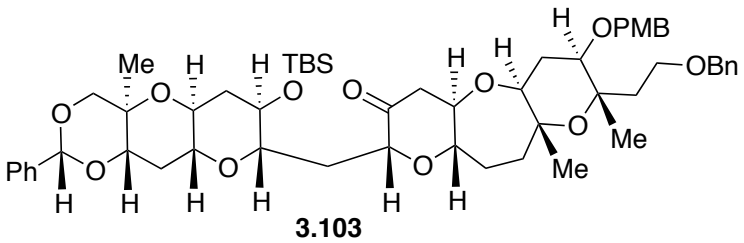
2H), 5.88 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.52 (s, 1H), 5.13 (dd, *J* = 18.1, 1.0 Hz, 1H), 5.09 (d, *J* = 10.7 Hz, 1H), 4.99 (d, *J* = 6.3 Hz, 1H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.36 (d, *J* = 10.7 Hz, 1H), 3.89 (d, *J* = 10.3 Hz, 1H), 3.79 (s, 3H), 3.75 (dd, *J* = 6.2, 6.2 Hz, 1H), 3.72-3.58 (m, 5H), 3.55 (ddd, *J* = 9.8, 9.8, 4.4 Hz, 1H), 3.48 (partially obscured ddd, *J* =10.8, 9.3, 3.9 Hz, 1H), 3.44 (partially obscured dd, *J* =11.7, 4.4 Hz, 1H), 3.36 (dd, *J* = 12.2, 3.9 Hz, 1H), 3.19 (ddd, *J* = 10.7, 9.3, 4.4 Hz, 1H), 2.87 (dd, *J* = 14.9, 2.7 Hz, 1H), 2.39 (dd, *J* = 14.9, 9.5 Hz, 1H), 2.31-2.23 (m, 3H), 2.16 (ddd, *J* = 11.2, 3.9, 3.9 Hz, 1H), 2.12 (ddd, *J* = 12.2, 3.9, 3.9 Hz, 1H), 1.97-1.64 (m, 8H), 1.59-1.48 (m, 1H), 1.50 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 170.8, 159.4, 139.3, 138.0, 134.8, 131.1, 129.3, 129.2, 128.5, 128.4, 127.8, 127.6, 126.6, 117.2, 113.8, 103.1, 82.6, 80.5, 80.1, 79.9, 78.9, 78.2, 77.1, 76.3, 76.2, 75.4, 73.0, 71.0, 70.4, 70.0, 69.4, 66.8, 55.4, 42.0, 39.6, 39.2, 38.3, 36.6, 30.7, 28.9, 25.8, 23.6, 22.0, 19.8, 18.0, 15.1, -4.1, -4.8; IR (neat) 2932, 2859, 1735, 1613, 1514, 1456, 1378, 1250, 1092 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{56}H_{78}O_{12}SiNa$ 993.5 ($M+Na^+$), found 993.5.



3.100

Preparation of enol ether 3.100. To a solution of $TiCl_4$ (0.245 mL, 2.23 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added THF (1.18 mL, 13.4 mmol) dropwise. To the yellow solution TMEDA (2.03 mL, 13.4 mmol) was added dropwise and the solution turned to a red-brown color. The ice bath was then removed and the mixture was allowed to stir for 15 min. Activated Zn dust (330 mg, 5.08 mmol) and $PbCl_2$ (74.0 mg, 0.266

mmol) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3-5 min. To the slurry was transferred a solution of ester **3.99** (67.8 mg, 0.0699 mmol) and CH_3CHBr_2 (0.200 mL, 2.23 mmol) in CH_2Cl_2 (5 mL) via cannula. The reaction mixture was then heated to reflux for 30 min before it was cooled to 0 °C and quenched with sat. K_2CO_3 (aq., 1.0 mL). After stirring for 30 min at 0 °C, the resulting mixture was filtered through a piece of filter paper. The filtrate was concentrated and flash chromatography (10:1 hexanes:ethyl acetate) gave **3.100** as a colorless oil (32.9 mg, 50%). R_f 0.20 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -40.3° (c = 0.29, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.48-7.45 (m, 2H), 7.40-7.32 (m, 7H), 7.30-7.26 (m, 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.56 (s, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.52 (br d, *J* = 3.4 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* = 11.2 Hz, 1H), 3.90 (d, *J* = 10.2 Hz, 1H), 3.78 (s, 3H), 3.67-3.60 (m, 2H), 3.60-3.52 (m, 2H), 3.50-3.40 (m, 5H), 3.37 (dd, *J* = 12.2, 3.9 Hz, 1H), 3.31 (ddd, *J* = 9.3, 9.3, 2.0 Hz, 1H), 3.12 (ddd, *J* =11.2, 9.3, 4.4 Hz, 1H), 2.54 (d, *J* = 15.1 Hz, 1H), 2.28 (br d, *J* = 16.6 Hz, 1H), 2.21 (ddd, *J* = 11.2, 4.4, 4.4 Hz, 1H), 2.16 (ddd, *J* = 11.7, 3.9, 3.9 Hz, 1H), 2.13 (ddd, *J* = 12.2, 3.9, 3.9 Hz, 1H), 2.05-1.66 (m, 10H), 1.50 (s, 3H), 1.47 (ddd, *J* = 10.7, 10.7, 10.7 Hz, 1H), 1.24 (s, 3H), 1.19 (s, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 159.4, 151.6, 139.3, 138.1, 131.1, 129.4, 129.2, 128.5, 128.4, 1279, 127.6, 126.5, 113.8, 103.0, 94.8, 80.6, 80.0, 79.9, 79.7, 79.1, 78.8, 78.0, 77.0, 76.4, 75.6, 73.0, 70.8, 70.7, 69.9, 69.5, 66.5, 55.4, 41.9, 40.0, 39.9, 35.9, 30.7, 29.7, 29.4, 28.8, 25.8, 23.5, 22.5, 18.0, 15.1, -4.1, -4.8; IR (neat) 2933, 2859, 1651, 1513, 1458, 1377, 1250, 1093 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{55}H_{76}O_{11}SiNa$ 963.5 ($M+Na^+$), found 963.6.

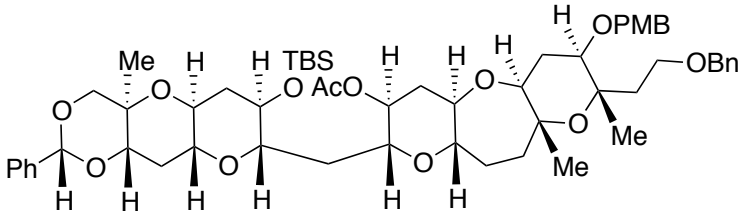


3.103

Preparation of ketone 3.103. To a solution of **3.100** (28.6 mg, 0.0304 mmol) in CH_2Cl_2 (5 mL) at -78 ^oC was added a solution of dimethyl dioxirane (0.61 mL of 0.10 M solution in CH_2Cl_2, 0.061 mmol) dropwise. The reaction mixture was warmed to 0 ^oC and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and the reaction mixture was cooled to -78 ^oC, at which temperature, a solution of DIBAL-H (0.304 mL of 1.0 M solution in THF, 0.304 mmol) was added. After stirring for 2 h at -78 ^oC, the reaction was quenched with sat. NH_4Cl (aq., 3 mL) and allowed to warm to rt. Saturated potassium sodium tartrate solution (10 mL) was added and the mixture was stirred violently for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided major alcohol **3.101** (17.5 mg, 60%) and minor alochol (6.1 mg, 21%) both as colorless oil.

To a solution of **3.101** (17.5 mg, 0.0183 mmol) in CH_2Cl_2 (5 mL) was added activated 4Å MS (20 mg), NMO (21.4 mg, 0.183 mmol) and TPAP (1 mg, 0.003 mmol). The reaction mixture was stirred at rt for 2 h before the solvent was removed in vacuo. Flash chromatography (5:1 hexanes:ethyl acetate) gave ketone **3.103** as a colorless oil (17.4 mg, 100%). R_f 0.55 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -42.0° (c = 0.10, THF); ^1H NMR (500 MHz, C_6D_6) δ 7.60 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.26-7.06 (m, 9H), 6.79 (d, *J* = 7.8 Hz, 2H), 5.39 (s, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.41 (d, *J* = 11.2

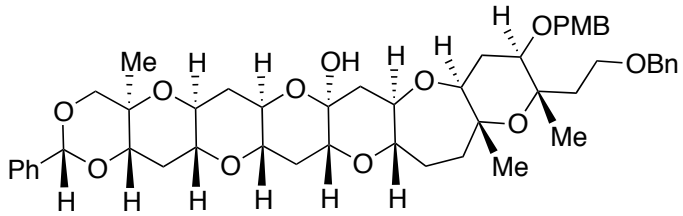
Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.25 (d, *J* = 11.2 Hz, 1H), 4.08 (dd, *J* = 7.3, 3.4 Hz, 1H), 3.92 (d, *J* = 10.2 Hz, 1H), 3.78-3.70 (m, 2H), 3.66-3.60 (m, 1H), 3.56-3.50 (partially obscured m, 1H), 3.53 (partially obscured d, *J* = 10.2 Hz, 1H), 3.45-3.25 (m, 4H), 3.28 (s, 3H), 3.16 (ddd, *J* = 8.3, 8.3, 4.4 Hz, 1H), 3.08-3.00 (m, 2H), 2.97 (dd, *J* = 15.6, 6.4 Hz, 1H), 2.76 (ddd, *J* =13.2, 7.8, 2.4 Hz, 1H), 2.36-2.22 (m, 3H), 2.16-2.00 (m, 4H), 2.00-1.88 (m, 2H), 1.86-1.62 (m, 6H), 1.43 (s, 3H), 1.33 (s, 3H), 1.18 (s, 3H), 0.98 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 205.1, 159.6, 139.4, 138.4, 131.0, 129.2, 128.9, 128.4, 128.2, 127.4, 126.7, 114.0, 102.8, 81.0, 80.2, 80.1, 79.8, 79.5, 79.4, 78.9, 78.3, 76.9, 76.4, 75.7, 73.0, 71.7, 70.6, 69.9, 69.5, 66.5, 54.6, 46.1, 42.2, 40.2, 39.6, 36.7, 33.3, 31.0, 30.1, 29.2, 28.8, 25.8, 24.8, 22.8, 22.6, 18.0, 15.1, -4.1, -4.8; IR (neat) 2931, 2858, 1727, 1513, 1460, 1377, 1250, 1092 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{55}H_{78}O_{12}SiK$ 995.5 ($M+K^+$), found 995.5.



3.102

Preparation of acetate 3.102. To a solution of **3.101** (25.6 mg, 0.0267 mmol) in CH_2Cl_2 (8 mL) were successively added Et_3N (37.2 μL, 0.267 mmol), Ac_2O (12.6 μL, 0.133 mmol), and DMAP (3.3 mg, 0.027 mmol). The reaction mixture was stirred for 2 h before it was quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided **3.102** as a colorless oil (21.7 mg, 81%). R_f 0.60 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -

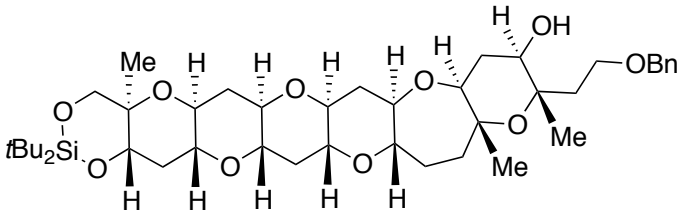
24.9° (c = 0.24, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.60 (d, *J* = 7.3 Hz, 2H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.24-7.08 (m, 8H), 6.79 (d, *J* = 7.8 Hz, 2H), 5.39 (s, 1H), 4.99 (ddd, *J* = 10.7, 10.7, 4.4 Hz, 1H), 4.52 (d, *J* = 11.2 Hz, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 4.37 (d, *J* = 13.2 Hz, 1H), 4.34 (d, *J* = 12.2 Hz, 1H), 3.92 (d, *J* = 9.8 Hz, 1H), 3.76 (dd, *J* = 15.6, 7.3 Hz, 1H), 3.68-3.50 (m, 6H), 3.50-3.37 (m, 2H), 3.30 (s, 3H), 3.20-3.01 (m, 4H), 2.77 (ddd, *J* = 11.7, 4.4, 4.4 Hz, 1H), 2.44 (ddd, *J* =12.2, 3.9, 3.9 Hz, 1H), 2.38-2.30 (m, 2H), 2.16-2.02 (m, 3H), 2.02-1.94 (m, 2H), 1.90 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.85-1.76 (m, 3H), 1.75 (s, 3H), 1.72-1.53 (m, 3H), 1.45 (s, 3H), 1.32 (s, 3H), 1.20 (s, 3H), 0.98 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 169.2, 159.6, 139.4, 138.5, 131.2, 129.3, 128.8, 128.4, 128.2, 127.4, 126.7, 114.0, 102.8, 81.5, 81.1, 79.9, 79.7, 79.3, 79.1, 78.3, 77.0, 76.4, 75.7, 73.0, 71.1, 70.6, 69.9, 69.6, 66.6, 54.7, 42.2, 40.4, 39.8, 37.7, 34.5, 30.9, 30.1, 29.5, 29.0, 25.9, 22.7, 22.6, 20.7, 18.0, 15.2, -3.9, -4.6; IR (neat) 2931, 2858, 1740, 1614, 1513, 1458, 1375, 1245, 1090 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{57}H_{80}O_{13}SiNa$ 1023.5 ($M+Na^+$), found 1023.5.



3.104

Preparation of hemiketal 3.104. To a solution of **3.103** (17.7 mg, 0.0185 mmol) in THF (10 mL) at 0 °C was slowly added HF•Py (0.60 mL, 33 mmol). The reaction mixture was allowed to warm up to rt and stirred for 2 d before it was quenched with sat. $NaHCO_3$ (aq., 50 mL). The aqueous phase was extracted with Ethyl acetate (3 x 10 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash

chromatography (2:1 hexanes:ethyl acetate) provided **3.104** as a colorless oil (15.5 mg, 99%). R_f 0.35 (2:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -15.8° (c = 0.22, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.48-7.45 (m, 2H), 7.39-7.24 (m, 8H), 7.23 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.56 (s, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 12.2 Hz, 1H), 4.36 (d, *J* = 10.7 Hz, 1H), 4.08 (br d, *J* = 6.8 Hz, 1H), 3.92 (d, *J* = 9.8 Hz, 1H), 3.80-3.74 (m, 1H), 3.78 (s, 3H), 3.68-3.62 (m, 2H), 3.59-3.44 (m, 4H), 3.42 (partially obscured dd, *J* = 11.7, 4.4 Hz, 1H), 3.33-3.27 (m, 1H), 3.22 (ddd, *J* = 11.7, 2.4, 1.5 Hz, 1H), 3.17 (ddd, *J* = 12.7, 9.3, 3.4 Hz, 1H), 3.13 (ddd, *J* = 11.2, 9.3, 3.9 Hz, 1H), 2.23-2.00 (m, 4H), 1.93-1.88 (m, 2H), 1.86-1.73 (m, 3H), 1.73-1.65 (m, 2H), 1.63-1.52 (m, 2H), 1.50 (s, 3H), 1.45 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.41-1.25 (m, 2H), 1.22 (s, 3H), 1.18 (s, 3H), 1.16-1.95 (m, 1H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 138.0, 131.0, 129.3, 129.2, 128.4, 127.8, 127.5, 126.5, 113.8, 103.0, 93.9, 82.2, 81.9, 79.8, 79.6, 79.3, 78.6, 77.6, 77.0, 76.3, 75.6, 72.9, 70.8, 70.2, 68.9, 66.5, 55.4, 49.2, 43.2, 41.8, 39.7, 35.3, 34.1, 30.6, 30.2, 29.2, 28.8, 25.8, 25.2, 22.4, 22.2, 15.0; IR (neat) 3323, 3055, 2927, 1624, 1433, 1265, 1113 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{49}H_{62}O_{12}Na$ 865.4 ($M+Na^+$), found 865.4.



3.107

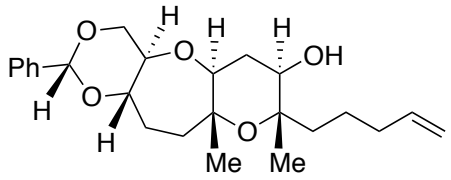
Preparation of the ATX A-F ring system 3.107. To a solution of **3.104** (15.9 mg, 0.0189 mmol) in CH_2Cl_2 (6 mL) and EtSH (2 mL) was added $Zn(OTf)_2$ (140 mg, 0.385 mmol). The reaction mixture was heated to reflux for 12 h before it was cooled

to rt and quenched with sat. $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (20:1 dichloromethane:methanol) provided triol **3.105** as a colorless oil.

To the solution of the triol obtained above in DMF (10 mL) at -20 °C was added tBu$_2$Si(OTf)$_2$ (14.0 μL, 0.0384 mmol). The reaction mixture was stirred at -20 °C for 1 h before pyridine (6.2 mL, 0.077 mmol) was added. The mixture was stirred for another 5 min and quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) provided a colorless oil which was taken to the next step without further purification.

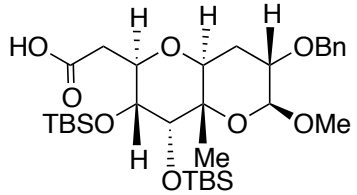
To the solution of the colorless oil obtained above in toluene (10 mL) was added Ph_3SnH (200 mg, 0.570 mmol). The reaction mixture was heated to reflux and AIBN (0.0046 M solution in toluene, 2.0 mL, 9.2 μmol) was added via syringe pump during 2 h. The mixture was then cooled to rt and solvent was removed under reduced pressure. Flash chromatography (2:1 hexanes:ethyl acetate) provided **3.107** as a colorless oil (7.3 mg, 51% 3 steps). R_f 0.20 (2:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -7.6° (c = 0.10, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.39-7.27 (m, 5H), 4.50 (s, 2H), 4.07 (dd, J = 12.2, 4.4 Hz, 1H), 3.88 (d, J = 10.2 Hz, 1H), 3.75 (d, J = 10.2 Hz, 1H), 3.59 (dd, J = 6.4, 4.4 Hz, 1H), 3.54 (dd, J = 12.2, 3.9 Hz, 1H), 3.40-3.35 (m, 1H), 3.33 (dd, J = 11.7, 3.9 Hz, 1H), 3.26 (ddd, J = 10.8, 9.3, 4.4 Hz, 1H), 3.19 (ddd, J = 12.7, 8.8, 4.4 Hz, 1H), 3.13-2.95 (m, 6H), 2.32-2.24 (m, 2H), 2.18-2.10 (m, 2H), 2.00-1.68 (m, 10H), 1.65 (ddd, J = 11.7, 11.7, 11.7 Hz, 1H), 1.42 (s, 3H), 1.41-1.34 (m, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.10 (s, 9H), 1.03 (s,

9H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 138.4, 129.0, 128.4, 128.4, 81.9, 81.4, 80.4, 78.6, 77.8, 77.7, 77.6, 77.4, 76.8, 75.0, 74.9, 74.3, 73.7, 73.2, 69.8, 67.1, 43.8, 40.5, 37.4, 35.9, 35.7, 34.0, 32.3, 29.9, 29.3, 28.0, 23.9, 20.4, 20.1, 15.6; IR (neat) 3417, 2925, 2855, 1652, 1457, 1375, 1080 cm^{-1}; FAB/MS (*m/z*) calcd for $C_{42}H_{66}O_{10}SiAg$ 865.3476 ($M+Ag^+$), found 865.3475.



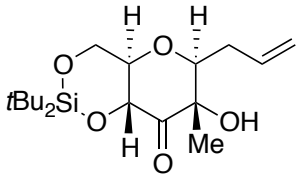
3.112

Characterization of alcohol 3.112. R_f 0.40 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +1.2° (c = 0.86, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.66 (dd, *J* = 7.7, 0.6 Hz, 2H), 7.21 (td, *J* = 7.7, 0.6 Hz, 2H), 7.14 (t, *J* = 7.7 Hz, 1H), 5.86 (dddd, *J* = 16.7, 10.2, 6.6, 6.6 Hz, 1H), 5.25 (s, 1H), 5.10 (dd, *J* = 16.7, 1.4 Hz, 1H), 5.02 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.29 (dd, *J* = 10.7, 5.2 Hz, 1H), 3.50-3.44 (m, 2H), 3.30 (ddd, *J* = 9.6, 9.6, 5.2 Hz, 1H), 3.27-3.22 (m, 1H), 2.99-2.95 (m, 1H), 2.07-1.95 (m, 3H), 1.86-1.66 (m, 5H), 1.66-1.47 (m, 3H), 1.40 (ddd, *J* = 10.7, 10.7, 3.0 Hz, 1H), 1.15 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.7, 139.2, 129.2, 128.7, 127.1, 115.0, 101.3, 83.5, 81.0, 77.3, 77.0, 75.5, 73.2, 70.2, 42.7, 39.9, 35.1, 33.3, 29.4, 23.1, 22.1, 21.4; IR (neat) 3388, 2979, 2870, 1496, 1297, 1214, 1101 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{24}H_{34}O_5Na$ 425.2 ($M+Na^+$), found 425.2.



3.119

Characterization of acid 3.119. R_f 0.40 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +37.6° (c = 1.0, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.22-7.15 (m, 4H), 7.10 (t, *J* = 7.8 Hz, 1H), 4.66 (s, 1H), 4.57 (dd, *J* = 13.2, 3.9 Hz, 1H), 4.47 (dd, *J* = 8.8, 8.8, 3.4 Hz, 1H), 4.22 (d, *J* = 12.2 Hz, 1H), 4.18 (d, *J* = 12.2 Hz, 1H), 3.90-3.88 (m, 1H), 3.86 (dd, *J* = 9.8, 2.4 Hz, 1H), 3.60 (dd, *J* = 2.9, 2.9 Hz, 1H), 3.13 (s, 3H), 2.84 (dd, *J* = 15.1, 3.4 Hz, 1H), 2.52 (dd, *J* = 15.1, 8.8 Hz, 1H), 2.10 (d, *J* = 12.7 Hz, 1H), 1.98 (ddd, *J* = 13.2, 13.2, 3.4 Hz, 1H), 1.48 (s, 3H), 1.09 (s, 9H), 0.94 (s, 9H), 0.31 (s, 3H), 0.25 (s, 3H), 0.07 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 178.0, 139.0, 128.8, 128.2, 128.1, 101.4, 78.3, 77.4, 76.8, 74.9, 72.2, 71.6, 68.6, 54.7, 38.2, 27.0, 26.9, 26.4, 19.4, 18.9, 18.8, -2.4, -2.5, -4.0, -4.2; IR (neat) 2931, 1715, 1466, 1253, 1115, 1066 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{31}H_{53}O_8Si_2$ 609.3 (M-H$^+$), found 609.3.



3.124

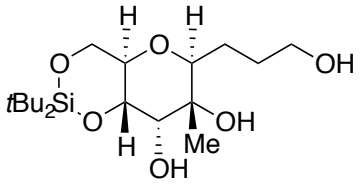
Preparation of ketone 3.124. To a solution of $(COCl)_2$ (0.53 mL, 6.2 mmol) in CH_2Cl_2 (40 mL) at -78 °C was added DMSO (0.58 mL, 8.2 mmol) dropwise. Then a solution of **3.122** (1.90 g, 4.08 mmol) in CH_2Cl_2 (10 mL) was cannulated into the reaction mixture. After stirring at -78 °C for 45 min, Et_3N (2.28 mL, 16.4 mmol) was added and the reaction was stirred for another 5 min. The reaction was quenched with sat. NH_4Cl (aq., 50 mL) and allowed to warm to rt. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (20:1 hexanes:ethyl acetate) provided the corresponding ketone (1.85 g, 98%) as a colorless oil.

To a solution of the ketone from above (1.80 g, 4.17 mmol) in 80 mL toluene at -90 ^{o}C was added MeLi (18.3 mL of 1.6 M in diethyl ether, 29.2 mmol) dropwise. After stirring for 1 h at -90 ^{o}C, the reaction was quenched with sat. NH_4Cl (aq., 50 mL) and allowed to warm to rt. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (20:1 hexanes:ethyl acetate) gave tertiary alcohol **3.123** (1.56 g, 84%) as a colorless oil.

To a solution of **3.123** (0.80 g, 1.67 mmol) in CH_2Cl_2 (27 mL) was added pH7 buffer (3 mL) and DDQ (0.76 g, 3.35 mmol). The reaction mixture was stirred at rt for 2 h before H_2O (20 mL) was added. The aqueous phase was extracted with ethyl acetate (3 x 15 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated. Flash chromatography (2:1 hexanes:ethyl acetate) gave the corresponding diol as a colorless oil (0.57 g, 95%).

To a solution of the diol from above (0.11g, 0.31 mmol) in a mixture of CH_2Cl_2 (6 mL) and DMSO (3 mL) were added Et_3N (0.21 mL, 1.65 mmol) and SO_3•Py (0.24 g, 1.65 mmol). The reaction mixture was stirred for 3 h at rt before it was quenched with H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) gave **32** as a colorless oil (0.10 g, 91%). R_f 0.60 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_{D}$ = -54.2° (c = 0.57, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (dddd, *J* = 17.0, 10.0, 6.6, 6.6 Hz, 1H), 4.98 (dd, *J* = 17.0, 1.3 Hz, 1H), 4.93 (d, *J* = 10.0 Hz, 1H), 4.56 (d, *J* = 9.7 Hz, 1H), 4.14 (dd, *J* = 10.2, 4.6 Hz, 1H), 3.98 (s, 1H), 3.89 (dd, *J* = 10.1, 10.1 Hz, 1H), 3.34 (ddd, *J* = 9.8, 9.8, 4.6 Hz, 1H), 3.18 (dd, *J* = 9.9, 2.1 Hz, 1H), 2.32 (dd, *J* = 14.4, 7.1 Hz, 1H), 2.13 (ddd, *J* = 16.1, 9.8, 6.4 Hz, 1H), 1.22 (s, 3H),

0.93 (s, 9H), 0.87 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 134.8, 117.2, 85.9, 78.4, 77.9, 77.7, 66.9, 32.9, 27.4, 27.1, 22.8, 20.2, 19.9; IR (neat) 3482, 2937, 2863, 1736, 1473, 1390, 1162, 1112 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{18}H_{32}O_5SiNa$ 379.2 ($M+Na^+$), found 379.2.



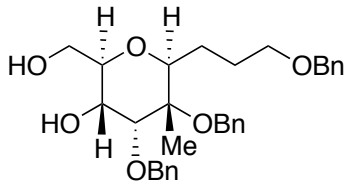
3.126

Preparation of triol 3.126. To a solution of **3.124** (1.56 g, 4.38 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added 2,6-lutidine (3.10 mL, 26.6 mmol) and TMSOTf (2.38 mL, 13.3 mmol). The reaction mixture was allowed to slowly warm up to rt over 2 h before it was quenched with H_2O (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (20:1 hexanes:ethyl acetate) gave the corresponding TMS ether as a colorless oil (1.90 g, 100%).

To a solution of the obtained TMS ether (1.90 g, 4.44 mmol) in THF (40 mL) at -78 °C was added L-selectride (6.66 mL of 1.0 M solution in THF, 6.66 mmol). The reaction mixture was allowed to slowly warm up to rt over 2 h before it was quenched with sat. NH_4Cl (aq., 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. The residue was passed through a plug of silica gel (10:1 hexanes:ethyl acetate) and concentrated. The resulted colorless oil was used directly in the next step without additional purification.

To a solution of the colorless oil obtained from above in THF (15 mL) at 0 °C was added BH_3•DMS (2.0 M solution in THF, 11.1 mL, 22.2 mmol). The reaction mixture

was stirred for 2 h at 0 °C before it was quenched by addition of H_2O (1.0 mL). To the reaction mixture was then added NaOH (25 mL of 3.0 M aq. solution,) followed by H_2O_2 (30 mL of 30% aq. solution,). The reaction mixture was then allowed to warm up to rt overnight. The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography gave **3.126** as a colorless oil (1.17 g, 70% over 2 steps). R_f 0.35 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -39.3° (c = 0.29, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (dd, *J* = 9.5, 4.6 Hz, 1H), 3.78 (dd, *J* = 9.3, 2.7 Hz, 1H), 3.73 (dd, *J* = 10.2, 10.2 Hz, 1H), 3.71-3.63 (m, 2H), 3.58-3.53 (m, 2H), 3.43 (d, *J* = 10.2 Hz, 1H), 3.40 (br s, 1H), 3.16 (br s, 1H), 3.07 (br s, 1H), 1.76 (ddd, *J* = 14.2, 7.1, 7.1 Hz, 1H), 1.71-1.62 (m, 1H), 1.60-1.50 (m, 1H), 1.29-1.21 (m, 1H), 1.08 (s, 3H), 0.98 (s, 9H), 0.95 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 78.9, 75.8, 74.3, 71.8, 70.9, 67.0, 62.5, 30.1, 27.6, 27.4, 24.6, 22.9, 20.4, 18.8; IR (neat) 3414, 2936, 2893, 2862, 1472, 1393, 1157, 1102 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{18}H_{36}O_6SiNa$ 399.2 ($M+Na^+$), found 399.3.

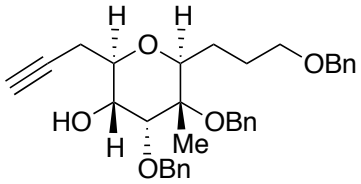


3.127

Preparation of diol 3.127. To a solution of **3.127** (1.17 g, 3.11 mmol) in THF (40 mL) was added KH (3.0 g of 30% dispersion in mineral oil, 22.5 mmol). The mixture was stirred at rt for 30 min before it was cooled to 0 °C. Then BnBr (4.22 mL, 35.5 mmol) was added dropwise and the reaction mixture was warmed up to rt and stirred overnight before it was quenched with sat. NH_4Cl (aq., 20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phase was dried (Na_2SO_4) and

concentrated to give a yellow oil which was taken to the next step without further purification.

The residue from above was dissolved in THF (20 mL) and cooled to 0 ^{o}C. To the solution was added HF•Py (1.0 mL, 55 mmol) and the reaction mixture was allowed to warm up to rt overnight. The reaction was quenched with sat. $NaHCO_3$ (aq., 20 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate) provided diol **3.127** (0.98 g, 61% over 2 steps) as a colorless oil. R_f 0.40 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -31.4° (c = 0.18, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.35 (m, 15H), 5.02 (d, *J* = 11.2 Hz, 1H), 4.80 (d, *J* = 11.2 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.66 (d, *J* = 11.5 Hz, 1H), 4.62 (s, 2H), 4.08 (d, *J* = 3.9 Hz, 1H), 3.98 (d, *J* = 10.2 Hz, 1H), 3.95 (partially obscured br d, *J* = 14.6 Hz, 1H), 3.88-3.76 (m, 2H), 3.70 (ddd, *J* = 10.0, 3.4, 3.4 Hz, 1H), 3.66-3.62 (m, 2H), 3.14-3.04 (m, 2H), 2.10-1.98 (m, 2H), 1.90-1.78 (m, 1H), 1.60-1.48 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.2, 139.1, 139.0, 128.8, 128.7, 128.0, 127.9, 127.8, 127.7, 127.3, 81.2, 78.1, 76.9, 76.8, 75.4, 73.1, 70.8, 68.0, 63.9, 63.2, 27.3, 25.3, 16.6; IR (neat) 3421, 2930, 2874, 1496, 1454, 1380, 1210, 1106 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{31}H_{38}O_6Na$ 529.3 ($M+Na^+$), found 529.3.



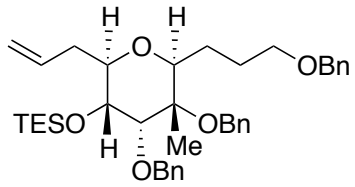
3.129

Preparation of alkyne 3.129. To a solution of **3.127** (0.57 g, 1.13 mmol) and 2,6-lutidine (0.495 mL, 4.25 mmol) in CH_2Cl_2 (20 mL) at -78 ^{o}C was added

trifluoromethanesulfonic anhydride (0.192 mL, 0.114 mmol). The reaction mixture was stirred for 30 min at -78 ^{o}C and TESOTf (0.288 mL, 0.127 mmol) was added. The reaction mixture was then slowly warmed to rt before it was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated to give a yellow oil. The oil was quickly passed through a plug of silica gel (10:1 hexanes:ethyl acetate) and concentrated to give the crude triflate **3.128**.

To a solution of trimethylsilylacetylene (0.690 mL, 4.88 mmol) in THF (20 mL) at 0 ^{o}C was added *n*BuLi (1.94 mL of 2.5 M solution in hexanes, 4.85 mmol). The reaction mixture was stirred at 0 ^{o}C for 30 min and then cooled to -78 ^{o}C. A solution of the crude **3.128** obtained from above and HMPA (0.900 mL, 5.17 mmol) in THF (10 mL) was cannulated into the reaction mixture. The reaction mixture was allowed to warm up to rt over 2 h before it was quenched with sat. NH_4Cl (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated to give a dark brown syrup which was taken up in THF (15 mL). To the solution was added TBAF (4.90 mL of 1.0 M solution in THF, 4.90 mmol) and the mixture was stirred at rt overnight before it was quenched with sat. NH_4Cl (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (4:1 hexanes:ethyl acetate) gave **3.129** as a colorless oil (0.34 g, 59% over 3 steps). R_f 0.20 (4:1 hexanes:ethyl acetate); $[\alpha]^{20}_{D}$ = -21.6° (c = 0.45, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42-7.27 (m, 15H), 5.01 (d, *J* = 11.0 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.56 (s, 2H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.02 (d, *J* = 1.7 Hz, 1H), 3.85 (d, *J* = 9.8 Hz, 1H), 3.64-

3.58 (m, 4H), 2.67 (ddd, *J* = 17.1, 2.4, 2.4 Hz, 1H), 2.47 (ddd, *J* = 17.1, 5.9, 2.7 Hz, 1H), 2.30-2.23 (m, 1H), 2.01 (t, *J* = 2.7 Hz, 1H), 2.00-1.90 (m, 2H), 1.81-1.70 (m, 1H), 1.50-1.40 (m, 1H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 138.9, 138.7, 128.8, 128.6, 128.5, 128.2, 128.0, 127.8, 127.6, 127.5, 127.1, 81.3, 81.2, 78.3, 77.0, 75.5, 75.2, 73.0, 70.8, 69.9, 64.0, 27.1, 25.1, 22.4, 16.2; IR (neat) 3420, 2928, 2873, 2119, 1606, 1496, 1454, 1378, 1209, 1104 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{33}H_{38}O_5K$ 553.3 ($M+K^+$), found 553.2.

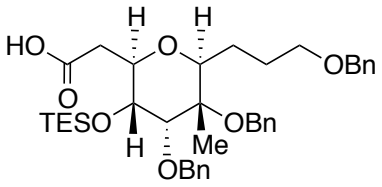


3.130

Preparation of alkene 3.130. To a solution of **3.129** (600 mg, 1.17 mmol) in CH_2Cl_2 (20 mL) at 0 ^oC was added 2,6-lutidine (0.272 mL, 2.34 mmol) and TESOTf (0.343 mL, 1.52 mmol). The reaction mixture was allowed to slowly warm up to rt over 3 h before it was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided the TES ether (732 mg, 100%) as a colorless oil.

To a solution of the TES ether obtained from above in ethyl acetate (30 mL) was added quinoline (70 μL, 0.59 mmol) and Lindlar's Pd catalyst (50 mg). The reaction mixture was stirred under H_2 atmosphere for 2 h before it was passed through a Celite plug with ethyl acetate. The filtrate was concentrated and flash chromatography (10:1 hexanes:ethyl acetate) gave **3.130** as a colorless oil (638 mg, 87%). R_f 0.50 (15:2 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +1.2° (c = 0.45, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.44

(d, *J* = 7.3 Hz, 2H), 7.33 (d, *J* = 7.3 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.20-7.04 (m, 9H), 6.08 (dddd, *J* = 17.1, 11.2, 6.8, 6.8 Hz, 1H), 5.19 (dd, *J* = 17.1, 1.9 Hz, 1H), 5.11 (d, *J* = 6.8 Hz, 1H), 5.08 (dd, *J* = 8.8, 1.9 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.42 (d, *J* = 10.7 Hz, 1H), 4.38 (d, *J* = 11.3 Hz, 1H), 4.29 (s, 2H), 4.05-4.00 (m, 2H), 3.82 (d, *J* = 2.4 Hz, 1H), 3.61 (dd, *J* = 9.3, 2.0 Hz, 1H), 3.39-3.31 (m, 2H), 2.68 (dd, *J* = 13.2, 6.8 Hz, 1H), 2.24 (ddd, *J* = 15.6, 7.8, 7.8 Hz, 1H), 2.06-1.95 (m, 2H), 1.70-1.60 (m, 1H), 1.56-1.48 (m, 1H), 1.19 (s, 3H), 1.00 (t, *J* = 7.8 Hz, 9H), 0.64 (q, *J* = 7.8 Hz, 6H), 0.30 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 140.3, 140.1, 139.9, 136.2, 128.9, 128.8, 128.8, 128.0, 127.9, 127.8, 127.8, 127.7, 117.0, 83.0, 78.0, 77.7, 76.4, 76.0, 74.7, 73.1, 71.1, 63.9, 37.3, 27.7, 26.0, 17.7, 7.7, 5.9; IR (neat) 2955, 2876, 1454, 1379, 1239, 1107, 1027 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{39}H_{54}O_5SiNa$ 653.4 ($M+Na^+$), found 653.4.

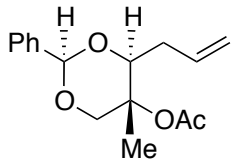


3.131

Preparation of acid 3.131. To a solution of **3.130** (638 mg, 1.01 mmol) in CH_2Cl_2 (60 mL) at -78 °C was bubbled through O_3 until the reaction developed a light blue color. The excess O_3 was purged from the reaction mixture by bubbling N_2 through it for 10 min until the light blue color completely dissappeared. Triphenylphosphine (1.33 g, 5.08 mmol) was then added and the mixture was allowed to slowly warm to rt. After 12 h, the solution was concentrated under reduced pressure. Flash chromatography (50:1 to 5:1 hexanes:ethyl acetate) provided the aldehyde (600 mg, 94%) as a colorless oil.

To a solution of the aldehyde obtained from above (600 mg, 0.949 mmol) in THF (10 mL) was successively added *t*BuOH (10 mL), H_2O (10 mL), 2-Me-2-butene (2.0

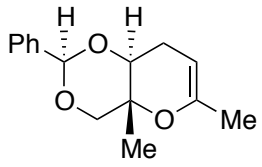
mL), NaH_2PO_4 (570 mg, 0.475 mmol) and $NaClO_2$ (430 mg, 0.475 mmol). The reaction mixture was stirred at 0 ^oC for 30 min and H_2O (30 mL) was added. The reaction mixture was extracted with ethyl acetate (3 x 15 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (1:1 hexanes:ethyl acetate to ethyl acetate) gave **3.131** (615 mg, 100%) as a colorless oil. R_f 0.50 (2:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -9.4° (c = 0.27, THF); ^1H NMR (500 MHz, C_6D_6) δ 11.7 (br s, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 2H), 7.19-7.03 (m, 9H), 5.09 (d, *J* = 11.2 Hz, 1H), 4.65 (d, *J* = 11.2 Hz, 1H), 4.52 (ddd, *J* = 8.8, 8.8, 3.4 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.37 (d, *J* = 11.2 Hz, 1H), 4.31 (s, 2H), 4.11 (d, *J* = 10.7 Hz, 1H), 3.82 (d, *J* = 2.0 Hz, 1H), 3.73 (dd, *J* = 9.2, 2.0 Hz, 1H), 3.40-3.32 (m, 2H), 2.86 (dd, *J* = 15.4, 3.2 Hz, 1H), 2.54 (dd, *J* = 15.4, 9.0 Hz, 1H), 2.02-1.92 (m, 2H), 1.72-1.62 (m, 1H), 1.50 (ddd, *J* = 9.3, 9.3, 9.3 Hz, 1H), 1.16 (s, 3H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.58 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 178.3, 140.1, 140.0, 139.9, 128.9, 128.8, 128.8, 128.1, 127.9, 127.8, 127.8, 127.7, 82.8, 78.0, 77.9, 76.0, 73.8, 73.8, 73.0, 70.8, 63.9, 38.2, 27.4, 25.7, 17.6, 7.6, 5.7; IR (neat) 3330, 2956, 2877, 1713, 1454, 1241, 1111 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{38}H_{52}O_7SiNa$ 671.4 ($M+Na^+$), found 671.3.



3.132

Preparation of acetate 3.132. To a solution of **3.55** (1.24 g, 5.30 mmol) in CH_2Cl_2 (25 mL) were successively added Et_3N (3.70 mL, 26.6 mmol), Ac_2O (1.50 mL, 15.6 mmol), and DMAP (0.646 g, 5.30 mmol). The reaction mixture was stirred for 2 h before it was quenched with sat. $NaHCO_3$ (aq., 20 mL). The aqueous phase was extracted

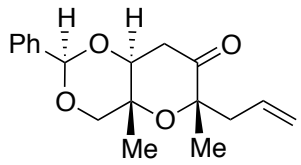
with CH_2Cl_2 (3 x 20 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided **3.132** as a colorless oil (1.15 g, 79%). R_f 0.60 (4:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -71.2° (c = 0.32, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.59 (d, *J* = 7.3 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 5.96 (dddd, *J* = 17.6, 10.3, 7.3, 6.3 Hz, 1H), 5.34 (s, 1H), 5.14 (d, *J* = 17.1 Hz, 1H), 5.08 (d, *J* = 10.3 Hz, 1H), 4.99 (d, *J* = 10.7 Hz, 1H), 3.73 (dd, *J* = 10.1, 2.7 Hz, 1H), 3.64 (d, *J* = 10.7 Hz, 1H), 2.40-2.33 (m, 1H), 2.29-2.21 (m, 1H), 1.69 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 168.8, 138.5, 135.2, 128.8, 128.2, 126.5, 116.8, 101.7, 81.6, 75.7, 74.2, 33.5, 21.1, 16.1; IR (neat) 2985, 2859, 1737, 1643, 1452, 1367, 1237, 1099 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{16}H_{20}O_4Na$ 299.1 ($M+Na^+$), found 299.1.



3.133

Preparation of enol ether 3.133. To a solution of $TiCl_4$ (7.37 mL, 67.2 mmol) in CH_2Cl_2 (440 mL) at 0 °C was added THF (35.5 mL, 0.404 mol) dropwise. To the yellow solution TMEDA (60.9 mL, 0.404 mol) was added dropwise and the solution turned to a red-brown color. The ice bath was then removed and the mixture was allowed to stir for 15 min. Activated Zn dust (9.83 g, 0.151 mol) and $PbCl_2$ (2.22 g, 7.98 mmol) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 10 min. To the slurry was transferred a solution of ester **3.132** (1.16 g, 4.20 mmol) and CH_3CHBr_2 (6.02 mL, 67.2 mmol) in CH_2Cl_2 (20 mL) via cannula. The reaction mixture was then

heated to reflux for 2 h before it was cooled to 0 °C and quenched with sat. K_2CO_3 (aq., 50 mL). After stirring for 30 min at 0 °C, the resulting mixture was filtered through a piece of filter paper. The filtrate was concentrated and flash chromatography (15:1 hexanes:ethyl acetate) gave **3.133** as a colorless oil (0.949 g, 92%). R_f 0.70 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +23.0° (c = 0.43, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.52 (d, *J* = 7.3 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 2H), 7.12 (t, *J* = 7.3 Hz, 1H), 5.37 (s, 1H), 4.22 (d, *J* = 4.4 Hz, 1H), 3.94 (d, *J* = 9.8 Hz, 1H), 3.65 (dd, *J* = 10.7, 6.4 Hz, 1H), 3.60 (d, *J* = 10.3 Hz, 1H), 2.12-1.98 (m, 2H), 1.61 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 148.5, 138.5, 128.8, 128.1, 126.6, 102.3, 92.9, 77.1, 75.7, 69.6, 24.0, 19.9, 15.3; IR (neat) 2921, 2859, 1673, 1453, 1378, 1312, 1150, 1093 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{15}H_{18}O_3Na$ 269.1 ($M+Na^+$), found 269.1.



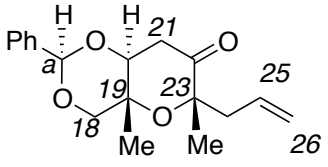
3.136

Preparation of ketone 3.136. To a solution of **3.133** (0.576 g, 2.34 mmol) in MeOH (30 mL) at -78 °C was added *m*CPBA (77%, 1.57 g, 7.00 mmol). The reaction mixture was slowly warmed up to 0 °C, at which point sat. $NaHCO_3$ (aq., 30 mL) was added. The mixure was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) provided **3.134** (0.550 g, 80%) as a white solid which was brought to the next step without further purification.

To a solution of **3.134** obtained above in THF (30 mL) were added NaH (88.0 mg, 3.67 mmol), allyl bromide (0.800 mL, 9.19 mmol), and TBAI (50.0 mg, 0.135

mmol). The reaction mixture was then heated to reflux overnight. After the reaction was cooled to rt, sat. NH_4Cl (aq., 20 mL) was added. The mixure was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. The residue was passed through a silica gel plug (5:1 hexanes:ethyl acetate). Concentration gave a colorless oil that was brought to the next step without further purification.

To the colorless oil obtained above in toluene (50 mL) were added pyridine (7.40 mL, 91.6 mmol) and PPTS (2.76 g, 11.0 mmol). The reaction mixture was heated to reflux for 16 h before it was cooled to rt and quenched with $NaHCO_3$ (aq., 30 mL). The mixure was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided **3.136** (0.409 g, 72% 2 steps). R_f 0.70 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = +11.2° (c = 0.43, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.50 (d, *J* = 7.3 Hz, 2H), 7.20 (t, *J* = 7.3 Hz, 2H), 7.14 (t, *J* = 7.3 Hz, 1H), 5.77 (dddd, *J* = 17.6, 10.3, 7.3, 7.3 Hz, 1H), 5.31 (s, 1H), 5.03 (d, *J* = 10.3 Hz, 1H), 4.99 (d, *J* = 17.6 Hz, 1H), 3.85 (d, *J* = 10.3 Hz, 1H), 3.81 (dd, *J* = 12.2, 7.0 Hz, 1H), 3.47 (d, *J* = 10.3 Hz, 1H), 2.61 (dd, *J* = 18.6, 6.8 Hz, 1H), 2.41 (dd, *J* = 18.6, 11.7 Hz, 1H), 2.30 (dd, *J* = 13.2, 7.5 Hz, 1H), 2.14 (dd, *J* = 13.7, 7.5 Hz, 1H), 1.25 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 208.8, 138.1, 133.0, 128.9, 128.2, 126.5, 119.1, 101.8, 83.8, 76.3, 68.3, 46.4, 39.4, 26.5, 17.1; IR (neat) 2982, 2865, 1716, 1521, 1456, 1372, 1143, 1114 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{18}H_{22}O_4Na$ 325.2 ($M+Na^+$), found 325.1.



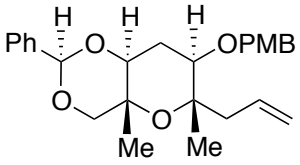
3.136

Summary of COSY spectrum for **3.136**

1. Proton at 5.77 ppm (C-25) shows cross peaks with protons at 5.03 ppm (C-26), 4.99 ppm (C-26'), 2.30 ppm (C-24) and 2.14 (C-24').
2. Proton at 3.85 ppm (C-18) shows cross peaks with proton at 3.47 ppm (C-18').
3. Proton at 3.81 ppm (C-20) shows cross peaks with protons at 2.61 ppm (C-21) and 2.41 ppm (C-21').
4. Proton at 2.61 ppm (C-21) shows cross peaks with proton at 2.41 ppm (C-21').
5. Proton at 2.30 ppm (C-24) shows cross peaks with proton at 2.14 ppm (C-24').

Summary of 1D nOe spectrum for **3.136**

1. Irradiation at 1.25 ppm (C-23 methyl) resulted in enhancement at 1.19 ppm (C-19 methyl) and 2.30 ppm (C-24) and 2.14 ppm (C-24').

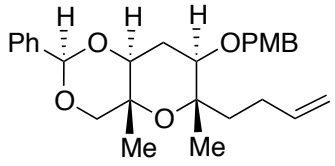


3.138

Preparation of PMB ether 3.138. To a solution of **3.136** (378 mg, 1.25 mmol) in MeOH (25 mL) at 0 ^{o}C was added $NaBH_4$ (190 mg, 5.02 mmol). The reaction mixture was quenched with acetone (10 mL) after stirring for 2 h at 0 ^{o}C. The solvent was then removed under reduced pressure and the residue was purified using flash chromatography (3:1 hexanes:ethyl acetate) to give **3.137** as a colorless oil (382 mg, 100%).

To a solution of **3.137** (382 mg, 1.25 mmol) in THF (20 mL) at 0 ^{o}C was added NaH (82.4 mg, 3.43 mmol), PMBBr (0.82 mL, 5.69 mmol), HMPA (0.220 mL, 1.15 mmol), and TBAI (50 mg, 0.135 mmol). The reaction mixture was stirred at rt for 12 h

before it was quenched with sat. NH_4Cl (aq., 20 mL). The mixure was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) gave **3.138** as a colorless oil (442 mg, 83%). R_f 0.55 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -32.8° (c = 0.30, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.64 (d, *J* = 7.8 Hz, 2H), 7.27-7.12 (m, 5H), 6.82 (d, *J* = 7.8 Hz, 2H), 6.07 (dddd, *J* = 17.1, 9.8, 7.3, 7.3 Hz, 1H), 5.39 (s, 1H), 5.14 (dd, *J* = 9.8, 1.3 Hz, 1H), 5.04 (dd, *J* = 17.6, 1.0 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.24 (d, *J* = 11.7 Hz, 1H), 3.85 (d, *J* = 9.7 Hz, 1H), 3.44 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.40 (d, *J* = 9.7 Hz, 1H), 3.32 (s, 3H), 3.23 (dd, *J* = 12.7, 3.4 Hz, 1H), 2.46 (dd, *J* = 13.7, 6.4 Hz, 1H), 2.33 (dd, *J* = 14.2, 7.8 Hz, 1H), 2.18 (ddd, *J* = 11.7, 3.9, 3.9 Hz, 1H), 1.85 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.53 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.7, 138.7, 135.0, 130.8, 129.3, 129.3, 128.8, 128.2, 126.7, 117.4, 114.0, 102.7, 80.6, 78.6, 77.7, 76.9, 71.5, 70.3, 68.9, 54.7, 46.6, 26.8, 23.3, 19.1; IR (neat) 2947, 2864, 1611, 1512, 1461, 1376, 1247, 1144, 1086 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{26}H_{32}O_5Na$ 447.2 ($M+Na^+$), found 447.2.



3.139

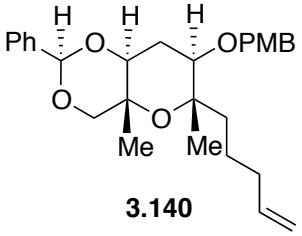
Preparation of PMB ether 3.139. To a solution of **3.138** (0.245 g, 0.578 mmol) in THF (15 mL) at 0 °C was added BH_3•DMS (0.870 mL of 2.0 M solution in THF, 1.74 mmol). The reaction mixture was stirred for 2 h at 0 °C before it was quenched by addition of H_2O (1.0 mL). To the reaction mixture was then added NaOH (2.0 mL of 3.0 M aq. solution) followed by H_2O_2 (5.0 mL of 30% aq. solution). The reaction mixture

was then allowed to warm up to rt overnight. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated.

To the crude product obtained from above in CH_2Cl_2 (15 mL) were sequentially added 4Å MS (0.60 g), NMO (0.680 g, 5.78 mmol), and TPAP (5 mg, 14.2 μmol). The reaction mixture was stirred at rt for 2 h before the solvent was removed in vacuo. The residue was filtered through a short sílica gel plug (5:1 hexanes:ethyl acetate) to give the crude aldehyde.

To a slurry of methyltriphenylphosphonium bromide (1.03 g, 2.88 mmol) in THF (10 mL) was added *t*BuOK (2.89 mL of 1.0 M solution in THF, 2.89 mmol). After stirring at rt for 30 min, the solution was transferred to a solution of the crude aldehyde from above in THF (10 mL). The reaction mixture was stirred at rt for 2 h before it was quenched with NH_4Cl (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The organic phase was combined, dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) gave **3.139** as a colorless oil (0.154 g, 61% for 3 steps). R_f 0.60 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -55.4° (c = 0.37, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.64 (d, *J* = 7.3 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 2H), 7.18-7.12 (m, 3H), 6.81 (d, *J* = 8.3 Hz, 2H), 5.85 (dddd, *J* = 17.1, 10.2, 6.8, 6.3 Hz, 1H), 5.42 (s, 1H), 5.09 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.00 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.20 (d, *J* = 11.7 Hz, 1H), 3.84 (d, *J* = 9.8 Hz, 1H), 3.39 (d, *J* = 10.8 Hz, 1H), 3.36 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.31 (s, 3H), 3.24 (dd, *J* = 12.2, 3.4 Hz, 1H), 2.24-2.12 (m, 3H), 1.86 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.81 (ddd, *J* = 13.2, 11.2, 5.4 Hz, 1H), 1.64 (ddd, *J* = 13.7, 11.2, 5.4 Hz, 1H), 1.53 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 160.2, 140.0, 139.2, 131.1, 129.9, 129.3, 128.7, 127.2, 114.6, 114.5, 103.2, 81.3, 79.5, 77.9,

77.5, 70.7, 69.3, 55.2, 42.1, 28.3, 27.1, 23.5, 19.6; IR (neat) 2943, 2863, 1639, 1513, 1460, 1375, 1248, 1086 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{27}H_{34}O_5K$ 477.2 ($M+K^+$), found 477.2.



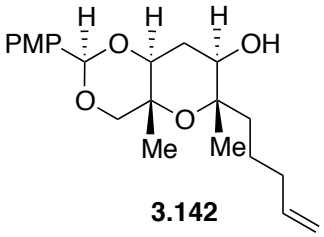
3.140

Preparation of PMB ether 3.140. To a solution of **3.139** (74.6 mg, 0.170 mmol) in THF (5 mL) at 0 ^oC was added BH_3•DMS (0.340 mL of 2.0 M solution in THF, 0.680 mmol). The reaction mixture was stirred for 2 h at 0 ^oC before it was quenched by addition of H_2O (1.0 mL). To the reaction mixture was then added NaOH (1.0 mL of 3.0 M aq. solution) followed by H_2O_2 (3.0 mL of 30% aq. solution). The reaction mixture was then allowed to warm up to rt overnight. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The combined organic phase was dried (Na_2SO_4) and concentrated.

To the crude product obtained from above in CH_2Cl_2 (10 mL) were sequentially added 4Å MS (0.20 g), NMO (0.200 g, 1.71 mmol), and TPAP (2.0 mg, 5.7 μmol). The reaction mixture was stirred at rt for 2 h before the solvent was removed in vacuo. The residue was filtered through a short silica gel plug (5:1 hexanes:ethyl acetate) to give the crude aldehyde.

To a slurry of methyltriphenylphosphonium bromide (300 mg, 0.840 mmol) in THF (5 mL) was added *t*BuOK (0.840 mL of 1.0 M solution in THF, 0.840 mmol). After stirring at rt for 30 min, the solution was transferred to a solution of the crude aldehyde from above in THF (5 mL). The reaction mixture was stirred at rt for 2 h before it was quenched with NH_4Cl (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x

10 mL). The organic phase was combined, dried (Na_2SO_4) and concentrated. Flash chromatography (15:1 hexanes:ethyl acetate) gave **3.140** as a colorless oil (42.1 mg, 55% for 3 steps). R_f 0.60 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -24.2° (c = 0.24, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.66 (d, *J* = 7.3 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 2H), 7.20-7.12 (m, 3H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.83 (dddd, *J* = 16.6, 9.8, 6.3, 6.3 Hz, 1H), 5.41 (s, 1H), 5.08 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.20 (d, *J* = 11.7 Hz, 1H), 3.85 (d, *J* = 9.8 Hz, 1H), 3.40 (d, *J* = 10.3 Hz, 1H), 3.37 (dd, *J* = 11.2, 4.9 Hz, 1H), 3.31 (s, 3H), 3.25 (dd, *J* = 12.2, 3.4 Hz, 1H), 2.20 (ddd, *J* = 9.7, 3.9, 3.9 Hz, 1H), 2.02-1.96 (m, 3H), 1.88 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.73-1.66 (m, 1H), 1.55 (s, 3H), 1.55-1.45 (m, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 159.7, 139.1, 138.7, 130.7, 129.5, 128.9, 128.2, 126.7, 114.5, 114.0, 102.7, 80.8, 78.9, 77.7, 77.1, 70.2, 68.8, 54.7, 42.0, 34.6, 26.6, 23.1, 22.6, 19.2; IR (neat) 2943, 2864, 1639, 1513, 1461, 1375, 1248, 1086 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{28}H_{36}O_5Na$ 475.3 ($M+Na^+$), found 475.2.



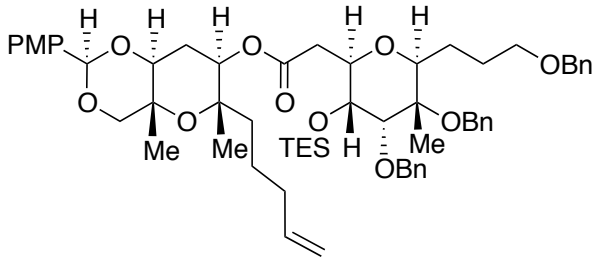
3.142

Preparation of alcohol 3.142. To a solution of **3.140** (42.1 mg, 93.1 μmol) in MeOH (5 mL) at 0 °C was added CSA (6.5 mg, 28.0 μmol). The reaction was warmed to rt for 5 h before it was quenched with $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were dried

(Na_2SO_4), and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) gave the diol as a colorless oil (29.3 mg, 86%).

To a solution of the diol in CH_2Cl_2 (4.5 mL) was added pH7 buffer (0.5 mL) and DDQ (36.5 mg, 0.161 mmol). The reaction mixture was stirred at rt for 2h before H_2O (5 mL) was added. The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated. Flash chromatography (2:1 hexanes:ethyl acetate) gave the triol **3.141** as a colorless oil (18.9 mg, 96%).

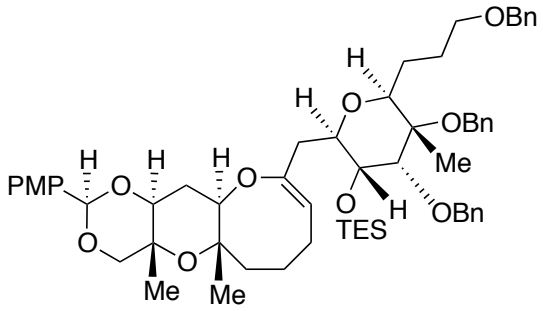
To a solution of the triol **3.141** in CH_2Cl_2 (5 mL) were added anisaldehyde dimethylacetal (19.8 μL, 0.116 mmol) and CSA (9.0 mg, 38.7 μmol). The reaction mixture was stirred at rt overnight before it was quenched with $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were dried (Na_2SO_4), and concentrated. Flash chromatography (3:1 hexanes:ethyl acetate) gave **3.142** as a colorless oil (24.8 mg, 88%). R_f 0.25 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -9.3° (c = 0.15, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.57 (d, *J* = 8.3 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 5.84 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.42 (s, 1H), 5.08 (d, *J* = 17.6 Hz, 1H), 5.02 (d, *J* = 10.3 Hz, 1H), 3.86 (d, *J* = 9.8 Hz, 1H), 3.42 (d, *J* = 9.8 Hz, 1H), 3.38 (dd, *J* = 12.2, 4.9 Hz, 1H), 3.30-3.26 (partially obscured m, 1H), 3.26 (s, 3H), 2.05-2.00 (m, 2H), 1.87 (ddd, *J* = 11.2, 4.4, 4.4 Hz, 1H), 1.80 (ddd, *J* = 11.7, 11.7, 11.7 Hz, 1H), 1.64-1.58 (m, 2H), 1.51 (s, 3H), 1.53-1.41 (m, 2H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 160.9, 139.6, 131.6, 128.5, 115.1, 114.2, 103.3, 81.3, 78.6, 77.5, 73.7, 69.4, 55.1, 42.6, 35.1, 31.4, 23.1, 22.2, 19.6; IR (neat) 3483, 2943, 2867, 1615, 1517, 1465, 1377, 1250, 1069 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{21}H_{30}O_5Na$ 385.2 ($M+Na^+$), found 385.2.



3.143

Preparation of ester 3.143. To a solution of acid **3.131** (53.4 mg, 82.2 μmol) in THF (8 mL) was added triethylamine (0.100 mL, 0.719 mmol) and 2,4,6-trichlorobenzoyl chloride (77.0 μL, 0.493 mmol). The reaction mixture was heated at 40 ^{o}C for 2 h before the solvent was removed in vacuo. To the resulting residue was cannulated a solution of alcohol **3.142** (24.8 mg, 68.5 μmol) in toluene (8 mL). DMAP (0.100 g, 0.820 mmol) was then added and the reaction mixture was heated at 40 ^{o}C for 2 h. The reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the organic extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (10:1 hexanes:ethyl acetate) provided ester **3.143** (57.4 mg, 84%) as a colorless oil. R_f 0.70 (4:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -26.2° (c = 0.29, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.55 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 7.3 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.20-7.05 (m, 9H), 6.82 (d, *J* = 8.3 Hz, 2H), 5.84 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.32 (s, 1H), 5.22 (dd, *J* = 11.2, 4.9 Hz, 1H), 5.11 (d, *J* = 11.2 Hz, 1H), 5.08 (dd, *J* = 15.6, 1.5 Hz, 1H), 5.02 (dd, *J* = 10.3, 1.0 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.49 (ddd, *J* = 10.3, 7.3, 3.4 Hz, 1H), 4.43 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 4.33 (s, 2H), 4.13 (d, *J* = 9.8 Hz, 1H), 3.99 (dd, *J* = 9.8, 2.0 Hz, 1H), 3.88 (d, *J* = 2.0 Hz, 1H), 3.80 (d, *J* = 9.8 Hz, 1H), 3.42-3.34 (m, 3H), 3.27 (s, 3H), 3.28-3.24 (partially obscured m, 1H), 2.86 (dd, *J* = 14.7, 3.4

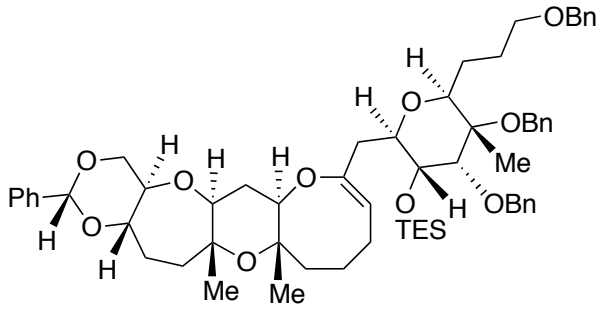
Hz, 1H), 2.62 (dd, *J* = 14.7, 7.3 Hz, 1H), 2.29 (ddd, *J* = 11.2, 4.4, 3.9 Hz, 1H), 2.08-1.96 (m, 5H), 1.80-1.55 (m, 6H), 1.49 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.00 (t, *J* = 8.3 Hz, 9H), 0.67 (q, *J* = 7.8 Hz, 3H), 0.66 (q, *J* = 8.3 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.7, 160.8, 140.2, 140.0, 139.8, 139.5, 131.6, 128.9, 128.8, 128.8, 128.5, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 115.1, 114.1, 103.1, 82.6, 80.5, 78.1, 78.0, 77.3, 77.1, 76.0, 74.3, 74.0, 73.2, 73.0, 71.0, 69.5, 63.9, 55.1, 42.4, 37.8, 34.9, 30.5, 28.2, 27.8, 26.1, 23.6, 23.0, 19.5, 17.6, 7.6, 5.8; IR (neat) 2954, 2876, 1741, 1496, 1379, 1249, 1106 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{59}H_{80}O_{11}SiNa$ 1015.6 ($M+Na^+$), found 1015.5.



3.144

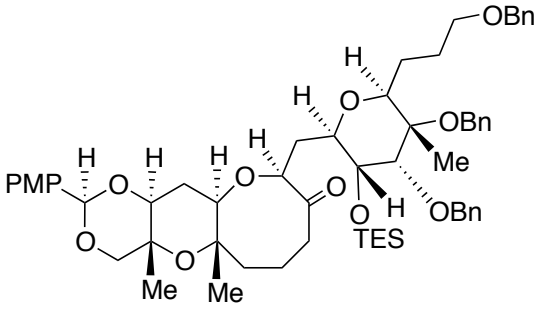
Preparation of enol ether 3.144. To a solution of $TiCl_4$ (0.230 mL, 2.09 mmol) in CH_2Cl_2 (13 mL) at 0 °C was added THF (1.10 mL, 12.5 mmol) dropwise. To the yellow solution TMEDA (1.90 mL, 12.5 mmol) was added dropwise and the solution turned to a red-brown color. The ice bath was then removed and the mixture was allowed to stir for 15 min. Activated Zn dust (304 mg, 4.68 mmol) and $PbCl_2$ (69.0 mg, 0.248 mmol) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3-5 min. To the slurry was transferred a solution of ester **3.143** (32.3 mg, 32.5 μmol) and CH_3CHBr_2 (0.190 mL, 2.12 mmol) in CH_2Cl_2 (3 mL) via cannula. The reaction mixture was then heated to reflux for 2 h before it was cooled to 0 °C and quenched with sat. K_2CO_3 (aq.,

1.0 mL). After stirring for 30 min at 0 °C, the resulting mixture was filtered through filter paper. The filtrate was concentrated and flash chromatography (10:1 hexanes:ethyl acetate) gave **3.144** as a colorless oil (12.5 mg, 40%). R_f 0.55 (5:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -14.1° (c = 0.28, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 7.3 Hz, 2H), 7.38 (d, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 2H), 7.21-7.06 (m, 9H), 6.83 (d, *J* = 8.3 Hz, 2H), 5.48 (s, 1H), 5.16 (d, *J* = 11.2 Hz, 1H), 4.90 (dd, *J* = 8.3, 2.9 Hz, 1H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.31 (s, 2H), 4.14 (d, *J* = 9.8 Hz, 1H), 3.98 (dd, *J* = 9.8, 4.9 Hz, 1H), 3.89 (d, *J* = 6.8 Hz, 1H), 3.88 (s, 1H), 3.69 (dd, *J* = 9.8, 2.2 Hz, 1H), 3.48 (d, *J* = 9.8 Hz, 1H), 3.44-3.38 (m, 2H), 3.27 (s, 3H), 3.28-3.22 (partially obscured m, 1H), 2.91 (d, *J* = 14.6 Hz, 1H), 2.30-1.97 (m, 8H), 1.84-1.70 (m, 2H), 1.69-1.56 (m, 3H), 1.55 (s, 3H), 1.36 (s, 3H), 1.24 (s, 3H), 1.01 (t, *J* = 7.8 Hz, 9H), 0.64 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 160.8, 155.7, 140.3, 140.1, 140.0, 131.8, 128.9, 128.8, 128.5, 128.0, 127.9, 127.9, 127.8, 127.7, 114.1, 108.1, 103.2, 84.0, 83.1, 81.3, 78.5, 78.0, 77.9, 77.8, 76.1, 74.9, 74.5, 73.1, 71.1, 69.4, 63.9, 55.1, 46.3, 40.2, 33.6, 31.0, 30.5, 28.5, 27.8, 25.9, 28.5, 27.8, 25.9, 22.4, 22.1, 19.8, 17.8, 7.6, 5.8; IR (neat) 2928, 2876, 1615, 1496, 1378, 1250, 1108 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{58}H_{78}O_{10}SiK$ 1001.6 ($M+K^+$), found 1001.5.



Characterization of the cyclic product from 3.146. R_f 0.45 (4:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -3.0° (c = 0.20, THF); ^{1}H NMR (400 MHz, C_6D_6) δ 7.68

(d, *J* = 7.3 Hz, 2H), 7.51 (d, *J* = 7.3 Hz, 2H), 7.39 (d, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 2H), 7.23-7.07 (m, 12H), 5.27 (s, 1H), 5.15 (d, *J* = 11.2 Hz, 1H), 4.88 (dd, *J* = 7.8, 3.4 Hz, 1H), 4.72 (d, *J* = 11.2 Hz, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.43 (d, *J* = 11.2 Hz, 1H), 4.41 (dd, *J* = 9.8, 9.8, 1H), 4.35-4.26 (m, 3H), 4.13 (d, *J* = 10.3 Hz, 1H), 3.90-3.84 (m, 2H), 3.69 (dd, *J* = 9.3, 2.0 Hz, 1H), 3.52-3.45 (m, 2H), 3.42-3.30 (m, 3H), 3.04 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.90 (d, *J* = 14.7 Hz, 1H), 2.32-2.22 (m, 2H), 2.12-1.96 (m, 6H), 1.92-1.52 (m, 9H), 1.34 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 1.02 (t, *J* = 7.8 Hz, 9H), 0.65 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 155.6, 140.4, 140.1, 140.1, 139.3, 136.5, 129.2, 128.9, 128.8, 128.8, 128.0, 128.0, 127.9, 127.8, 127.7, 127.1, 108.0, 101.3, 83.4, 83.4, 83.2, 80.9, 78.0, 77.8, 77.5, 77.0, 76.1, 75.6, 74.9, 74.4, 73.0, 71.1, 70.2, 63.9, 45.9, 40.2, 40.1, 33.0, 29.6, 28.2, 27.8, 26.0, 22.6, 22.3, 21.5, 17.8, 7.6, 5.8; IR (neat) 2924, 2855, 1456, 1376, 1105, 1027 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{61}H_{82}O_{10}SiK$ 1041.6 ($M+K^+$), found 1041.5.



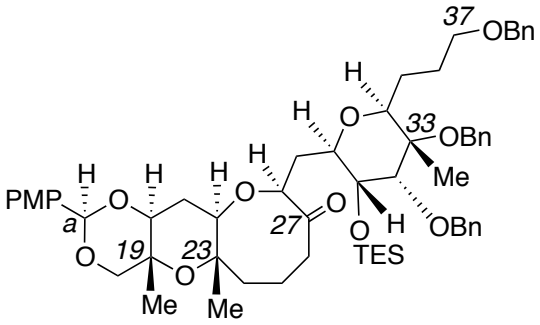
3.150

Preparation of ketone 3.150. To a solution of **3.144** (19.7 mg, 20.4 μmol) in CH_2Cl_2 (5 mL) at -78 °C was added a solution of dimethyl dioxirane (0.42 mL of 0.10 M solution in CH_2Cl_2, 0.042 mmol) dropwise. The reaction mixture was warmed to 0 °C and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (5 mL) and the reaction mixture was cooled to -78 °C, at which temperature, a solution of DIBAL-H

(0.21 mL of 1.0 M solution in THF, 0.21 mmol) was added. After stirring for 2 h at -78 ^{o}C, the reaction was quenched with sat. NH_4Cl (aq., 3 mL) and allowed to warm to rt. Saturated potassium sodium tartrate solution (10 mL) was added and the mixture was stirred violently for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated to give the crude alcohol.

To a solution of the crude alcohol obtained from above in CH_2Cl_2 (5 mL) were added activated 4Å MS (20 mg), NMO (25.0 mg, 0.213 mmol) and TPAP (1 mg, 0.003 mmol). The reaction mixture was stirred at rt for 2 h before the solvent was removed in vacuo. Flash chromatography (5:1 hexanes:ethyl acetate) gave ketone **3.150** as a colorless oil (12.2 mg, 61% 2 steps). R_f 0.55 (3:1 hexanes:ethyl acetate); $[\alpha]^{20}_{D}$ = -20.2° (c = 0.18, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.58 (d, *J* = 8.8 Hz, 2H), 7.46 (d, *J* = 7.3 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.21-7.06 (m, 9H), 6.83 (d, *J* = 8.3 Hz, 2H), 5.36 (s, 1H), 5.08 (d, *J* = 11.2 Hz, 1H), 4.70 (d, *J* = 11.2 Hz, 1H), 4.50 (dd, *J* = 9.3, 6.3 Hz, 1H), 4.44 (d, *J* = 11.2 Hz, 1H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.32 (s, 2H), 4.12 (ddd, *J* = 9.8, 6.8, 2.9 Hz, 1H), 4.09 (dd, *J* = 10.3, 1.5 Hz, 1H), 3.85 (d, *J* = 2.0 Hz, 1H), 3.81 (d, *J* = 9.8 Hz, 1H), 3.79 (dd, *J* = 9.8, 2.4 Hz, 1H), 3.44-3.33 (m, 4H), 3.27 (s, 3H), 3.14 (dd, *J* = 12.2, 3.0 Hz, 1H), 2.87 (ddd, *J* = 14.2, 7.8, 4.9 Hz, 1H), 2.31-2.06 (m, 5H), 2.04-1.94 (m, 3H), 1.84-1.70 (m, 2H), 1.64-1.54 (m, 3H), 1.52 (s, 3H), 1.34 (s, 3H), 1.24 (s, 3H), 1.03 (t, *J* = 7.8 Hz, 9H), 0.69 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 213.9, 160.9, 140.2, 140.1, 139.9, 131.6, 128.9, 128.8, 128.5, 128.0, 127.9, 127.9, 127.8, 127.7, 114.1, 103.1, 85.4, 83.3, 82.9, 81.4, 78.0, 77.9, 77.4, 76.0, 73.9, 73.2, 73.2, 71.1, 69.7, 63.9, 55.1, 44.0, 40.2, 35.4, 28.9, 27.8, 26.0, 21.5, 21.1, 20.2, 17.6, 7.6,

5.9; IR (neat) 2934, 2876, 1704, 1616, 1496, 1378, 1249, 1105 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{58}H_{78}O_{11}SiK$ 1017.6 ($M+K^+$), found 1017.5.



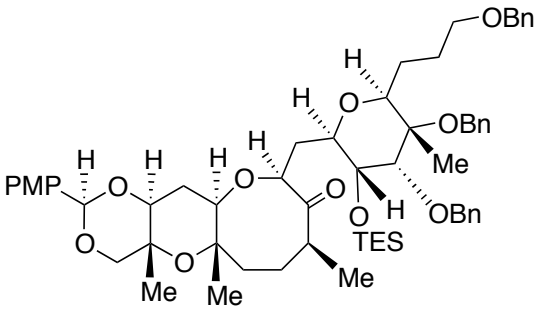
3.150

Summary of COSY spectrum for **3.150**

1. Proton at 4.50 ppm (C-28) shows cross peaks with proton at 2.28 ppm (C-29).
2. Proton at 4.12 ppm (C-30) shows cross peaks with proton at 3.79 ppm (C-31).
3. Proton at 4.09 ppm (C-34) shows cross peaks with protons at 1.62 ppm (C-35).
4. Proton at 3.81 ppm (C-18) shows cross peaks with proton at 3.40 ppm (C-18').
5. Proton at 2.06 ppm (C-21) shows cross peaks with proton at 3.36 ppm (C-22) and 3.14 (C-20).

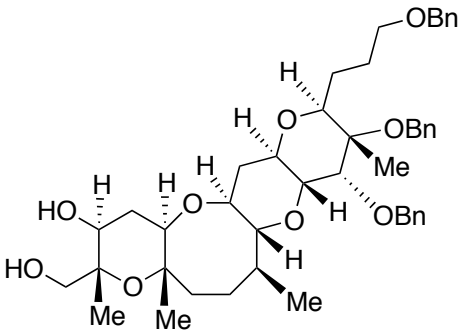
Summary of 1D nOe spectrum for **3.150**

1. Irradiation at 4.50 ppm (C-28) resulted in enhancement at 3.36 ppm (C-22).
2. Irradiation at 3.14 ppm (C-20) resulted in enhancement at 5.36 ppm (C-a), 3.40 ppm (C-18'), and 3.36 ppm (C-22).



3.151

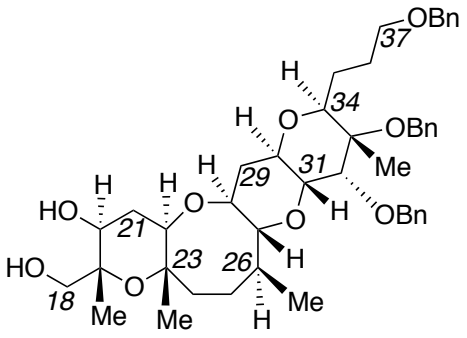
Preparation of ketone 3.151. To a solution of **3.150** (5.0 mg, 5.1 μmol) in THF (4 mL) at -78 °C was added LiHMDS (0.102 mL of 1.0 M solution in THF, 0.102 mmol). After 10 min, MeI (16 μL, 0.254 mmol) was added and the reaction mixture was allowed to slowly warm up to -22 °C before it was quenched with NH_4Cl (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (5:1 hexanes:ethyl acetate) provided **3.151** (4.7 mg, 93%) as a colorless oil. R_f 0.55 (3:1 hexanes:ethyl acetate). $[a]^{20}_D$ = -22.3° (c = 0.14, THF); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.36 (d, *J* = 8.8 Hz, 2H), 7.32-7.19 (m, 15H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.44 (s, 1H), 4.96 (d, *J* = 10.7 Hz, 1H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.46 (s, 2H), 4.32 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.85 (d, *J* = 1.5 Hz, 1H), 3.79 (s, 3H), 3.74 (d, *J* = 9.8 Hz, 1H), 3.68-3.52 (m, 3H), 3.52-3.40 (m, 5H), 2.99 (ddd, *J* = 7.8, 7.8, 7.8 Hz, 1H), 2.60-2.49 (m, 1H), 2.35-2.19 (m, 2H), 2.13 (ddd, *J* = 11.7, 3.9, 3.9 Hz, 1H), 1.95-1.50 (m, 8H), 1.50 (s, 3H), 1.36 (s, 3H), 1.28 (s, 3H), 1.20 (d, *J* = 7.3 Hz, 3H), 1.03 (t, *J* = 7.8 Hz, 9H), 0.71 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 214.2, 160.4, 139.6, 139.5, 131.1, 128.4, 128.3, 128.0, 127.5, 127.4, 127.3, 127.2, 113.6, 102.6, 85.4, 83.5, 82.4, 80.5, 77.4, 77.4, 77.0, 76.9, 75.5, 74.8, 73.1, 72.6, 70.5, 69.2, 63.4, 57.6, 54.6, 49.9, 44.7, 35.8, 30.0, 29.2, 28.4, 27.3, 25.5, 21.6, 21.3, 19.4, 17.2, 7.1, 5.3; IR (neat) 2956, 2876, 1718, 1616, 1496, 1377, 1249, 1104 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{59}H_{80}O_{11}SiNa$ 1015.6 ($M+Na^+$), found 1015.5.



3.152

Preparation of ATX F-I ring system 3.152. To a solution of **3.151** (4.7 mg, 4.7 μmol) in CH_2Cl_2 (3 mL) at -78 °C were added Et_3SiH (76 μL, 0.47 mmol) and TMSOTf (8.6 μL, 47.0 μmol). The reaction mixture was stirred at -78 °C for 1 h before it was allowed to slowly warm up to -50 °C, at which temperature the reaction was quenched with $NaHCO_3$ (aq., 5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (2:1 hexanes:ethyl acetate) provided **3.152** (2.8 mg, 80%) as a colorless oil. R_f 0.45 (1:1 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -1.1° (c = 0.05, THF); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.40-7.20 (m, 15H), 4.96 (d, *J* = 11.2 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 11.2 Hz, 1H), 4.43 (s, 2H), 4.40 (d, *J* = 11.2 Hz, 1H), 4.04 (d, *J* = 2.0 Hz, 1H), 3.82 (br d, *J* = 11.7 Hz, 1H), 3.71-3.64 (m, 2H), 3.49-3.46 (m, 2H), 3.41-3.35 (m, 2H), 3.29 (d, *J* = 10.7 Hz, 1H), 3.22 (ddd, *J* = 11.7, 8.8, 4.4 Hz, 1H), 3.12 (dd, *J* = 9.8, 2.0 Hz, 1H), 2.76 (dd, *J* = 9.3, 9.3 Hz, 1H), 2.30 (ddd, *J* = 11.2, 4.4, 4.4 Hz, 1H), 2.06-2.00 (m, 2H), 1.96 (ddd, *J* = 10.7, 4.4, 4.4 Hz, 1H), 1.95-1.35 (m, 11H), 1.28 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H), 1.08 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 140.1, 128.9, 128.8, 128.0, 127.9, 127.8, 127.7, 88.1, 86.2, 83.8, 80.8, 78.8, 78.7, 77.7, 77.2, 76.6, 75.0, 73.2, 71.1, 71.0, 69.1, 68.7, 63.8, 46.3, 40.7, 40.0, 33.9, 32.1, 30.5, 27.9, 26.0, 22.7, 20.3,

18.8, 17.9; IR (neat) 3500, 3028, 2925, 1599, 1494, 1451, 1264, 1077 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{45}H_{60}O_9K$ 783.4 ($M+K^+$), found 783.3.



3.152

Summary of COSY spectrum for **3.152**

1. Proton at 4.04 ppm (C-32) shows cross peaks with proton at 3.12 ppm (C-31).
2. Proton at 3.12 ppm (C-31) shows cross peaks with proton at 3.66 ppm (C-30).
3. Proton at 1.08 ppm (C-26 methyl) shows cross peaks with protons at 1.70 ppm (C-26).
4. Proton at 1.70 ppm (C-26) shows cross peaks with proton at 2.76 ppm (C-27).
5. Proton at 2.76 ppm (C-27) shows cross peaks with proton at 3.22 ppm (C-28).
6. Proton at 3.22 ppm (C-28) shows cross peaks with protons at 2.30 ppm (C-29) and 1.50 ppm (C-29').
7. protons at 2.30 ppm (C-29) and 1.50 ppm (C-29') both show cross peaks with proton at 3.66 ppm (C-30).

Summary of 1D nOe spectrum for **3.152**

1. Irradiation at 3.22 ppm (C-28) resulted in enhancement at 3.66 ppm (C-30), 3.40 ppm (C-22), 2.30 ppm (C-29), and 1.70 ppm (C-26).
2. Irradiation at 2.76 ppm (C-27) resulted in enhancement at 3.12 ppm (C-31), 1.50 ppm (C-29'), and 1.08 ppm (C-26 methyl).

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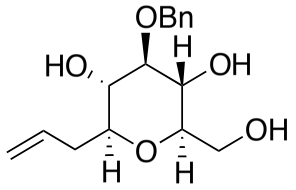
47 Our model studies have shown selective deprotection of the C37 benzyl group in the presence of the other two benzyl groups could be realized using DDQ.

APPENDIX A

^{1}H AND ^{13}C NMR SPECTRA CHAPTER 1



1.82

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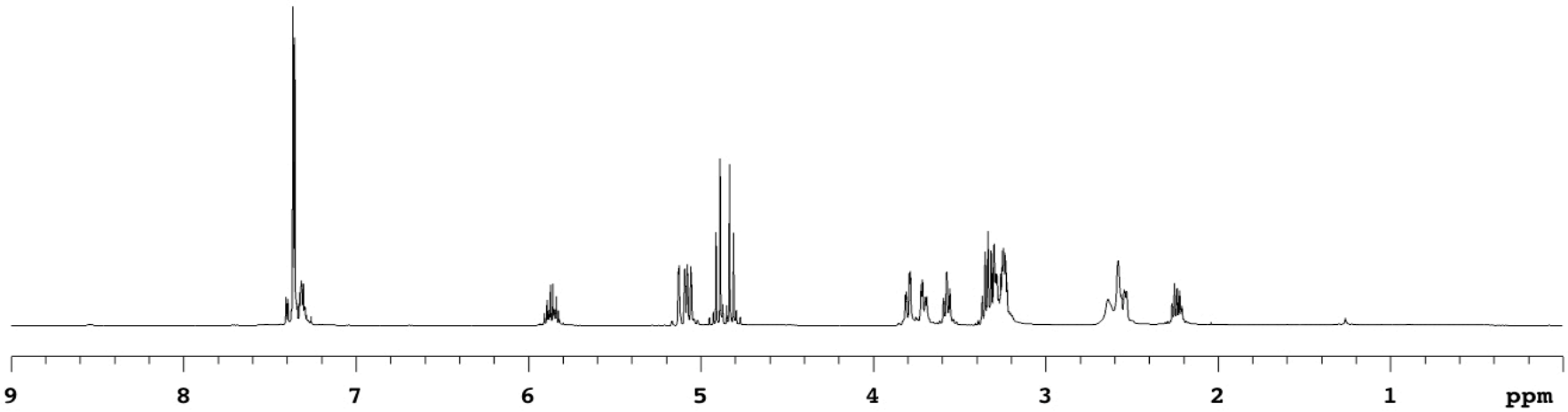

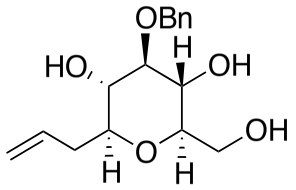

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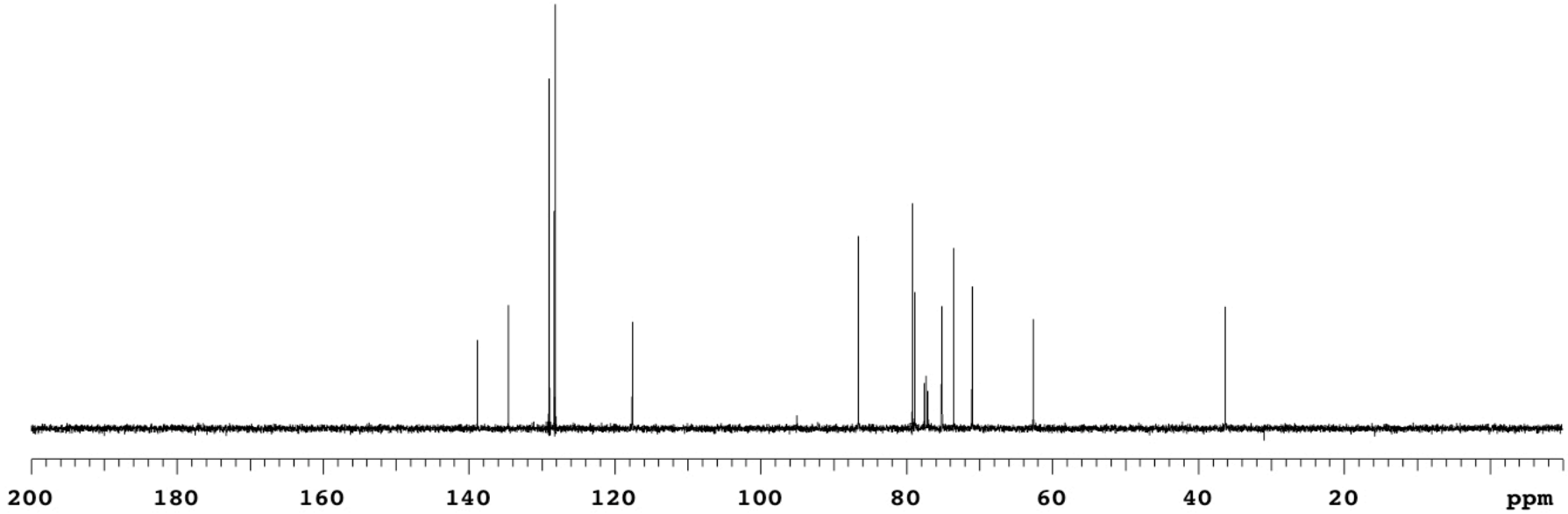

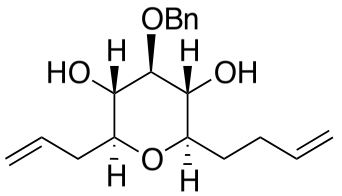

1.84

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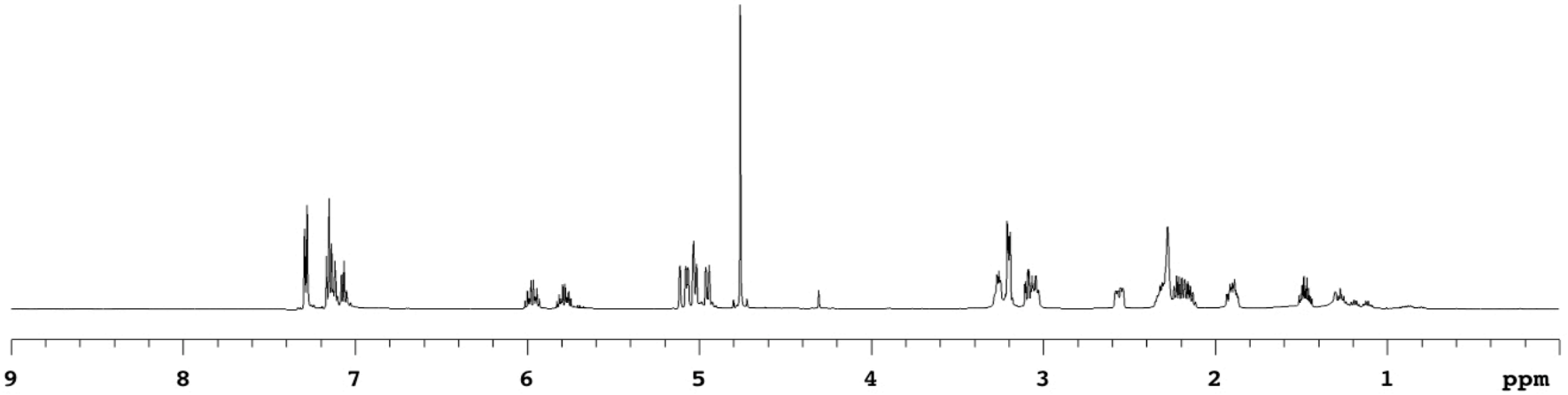

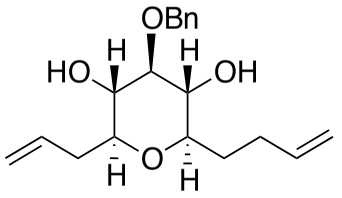

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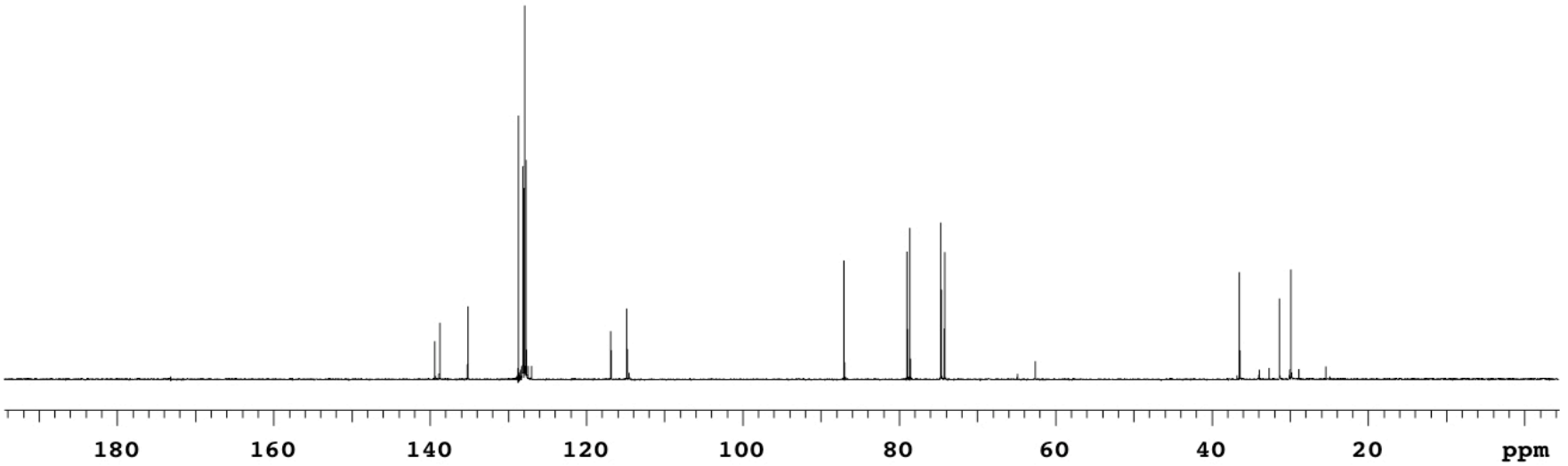
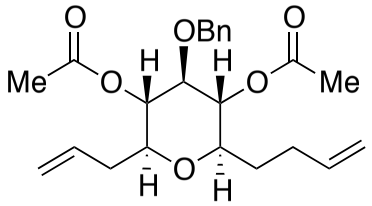
^{13}C NMR, 125 MHz, C_6D_6





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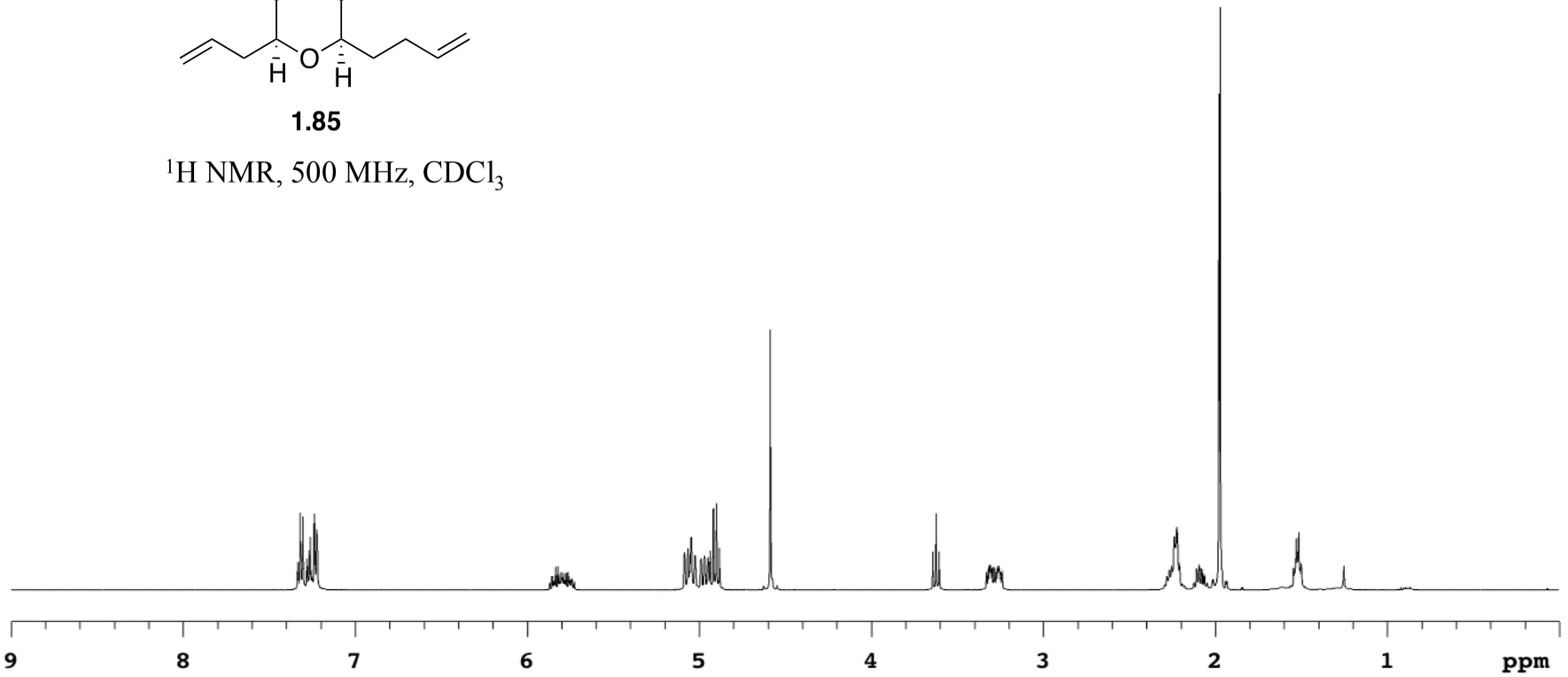
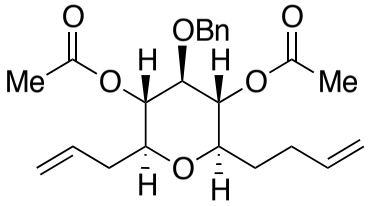
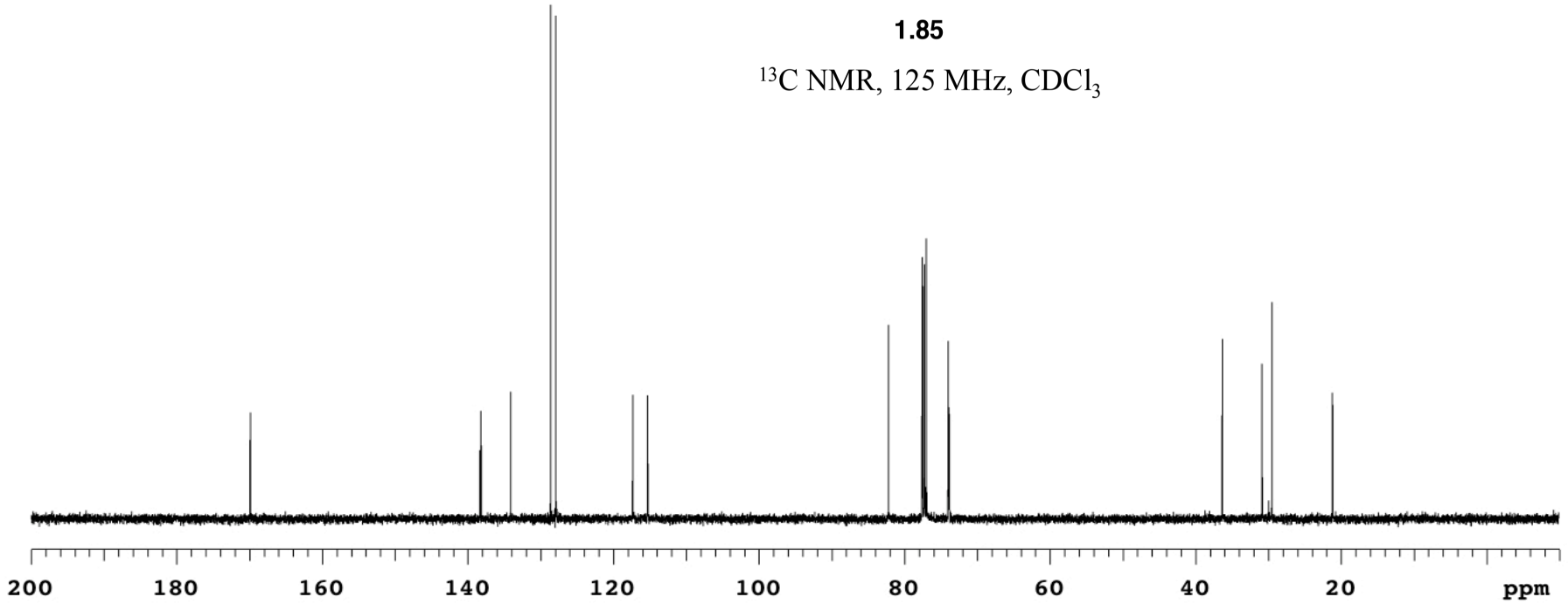
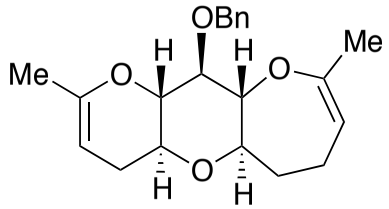




1.85

^{13}C NMR, 125 MHz, $CDCl_3$





1.86

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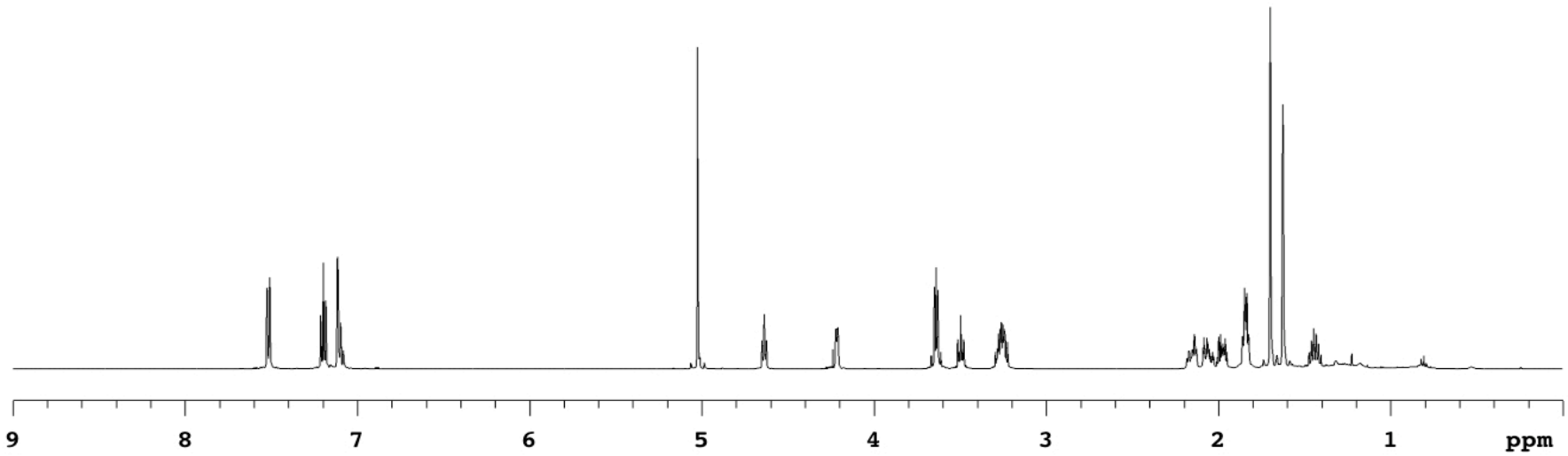

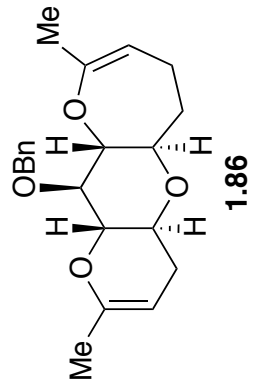

1.86

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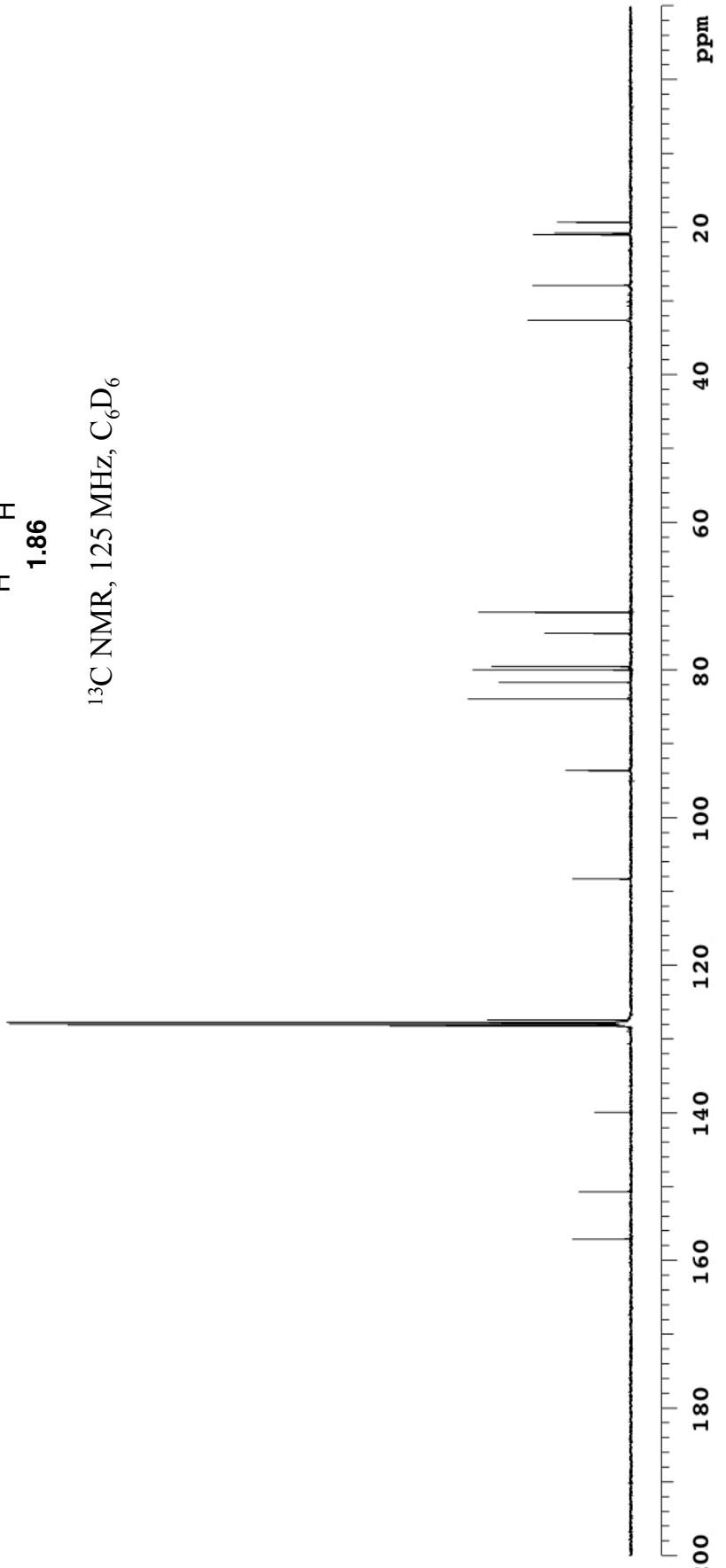

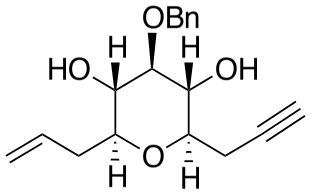

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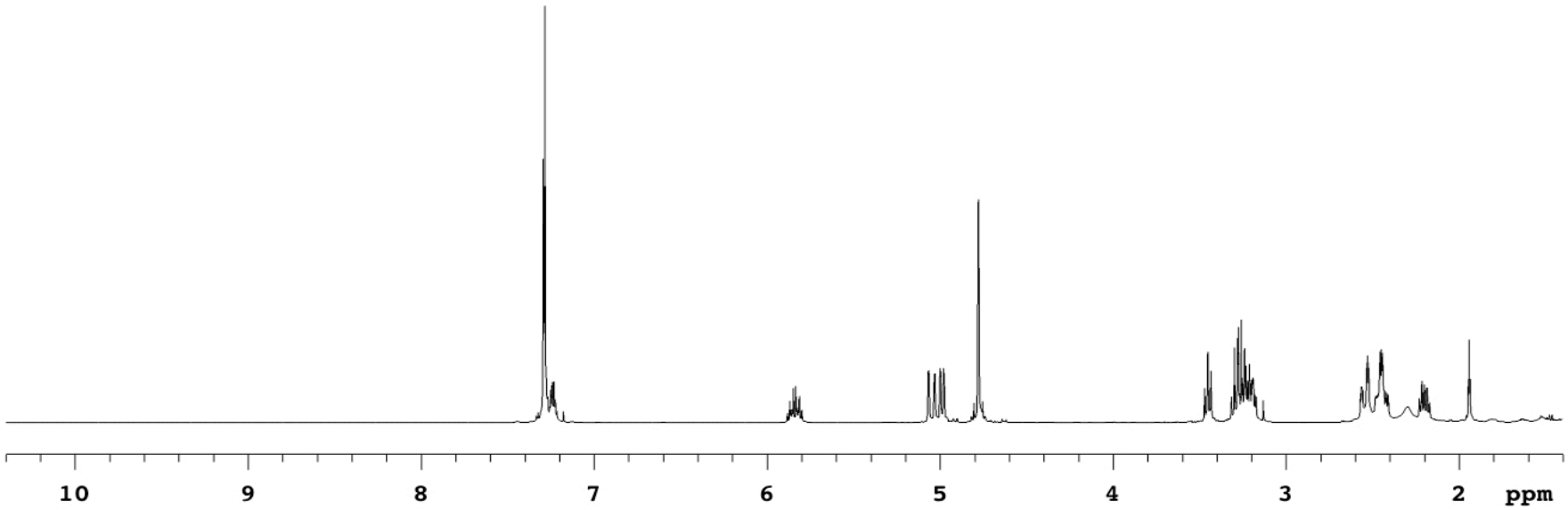
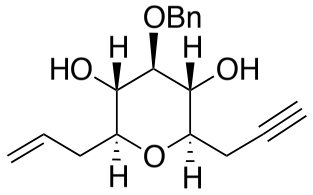
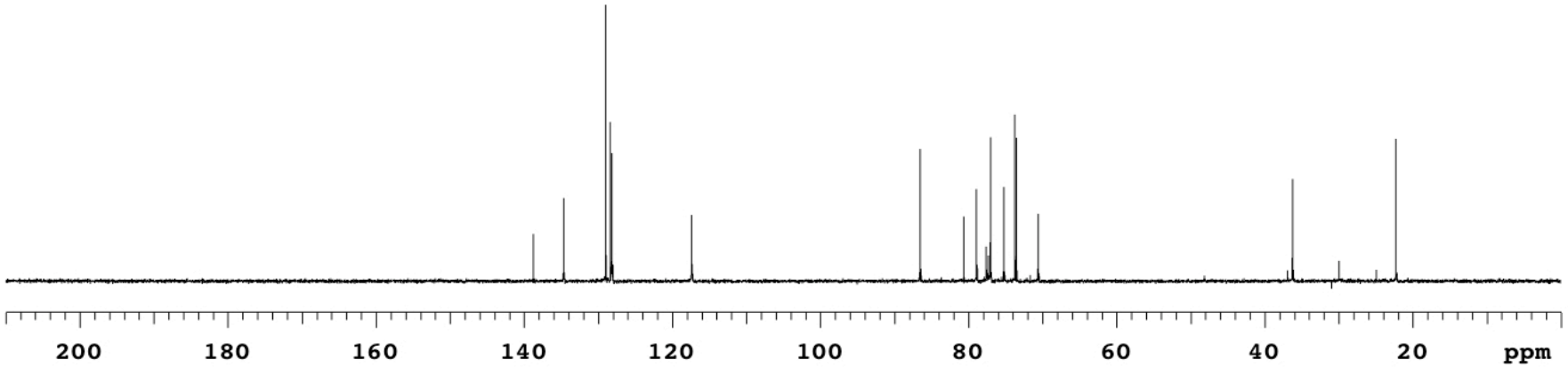
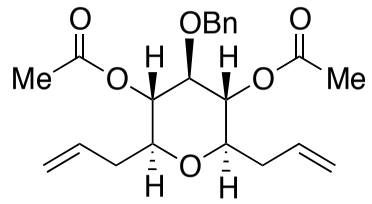




1.87

^{13}C NMR, 125 MHz, $CDCl_3$





1.89

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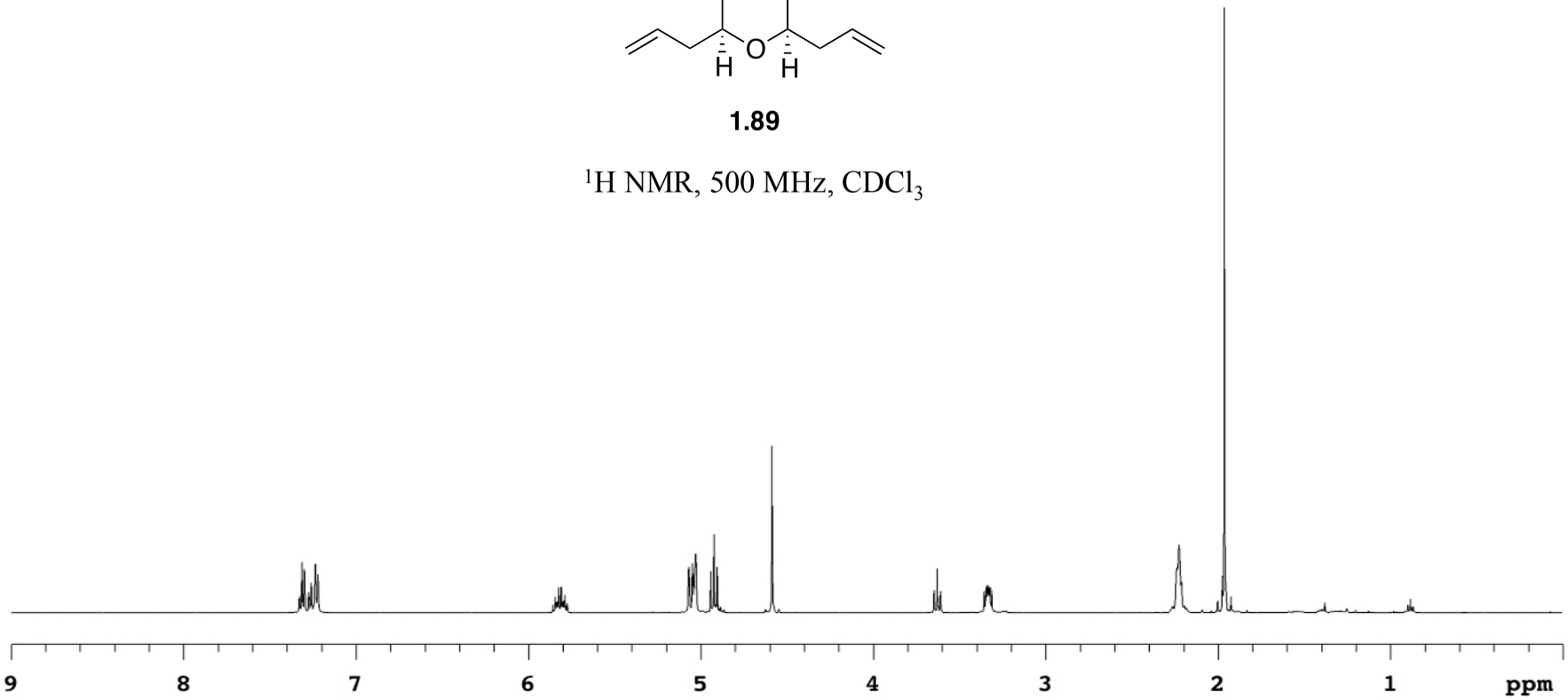

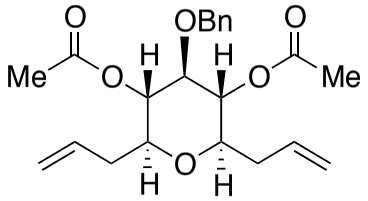

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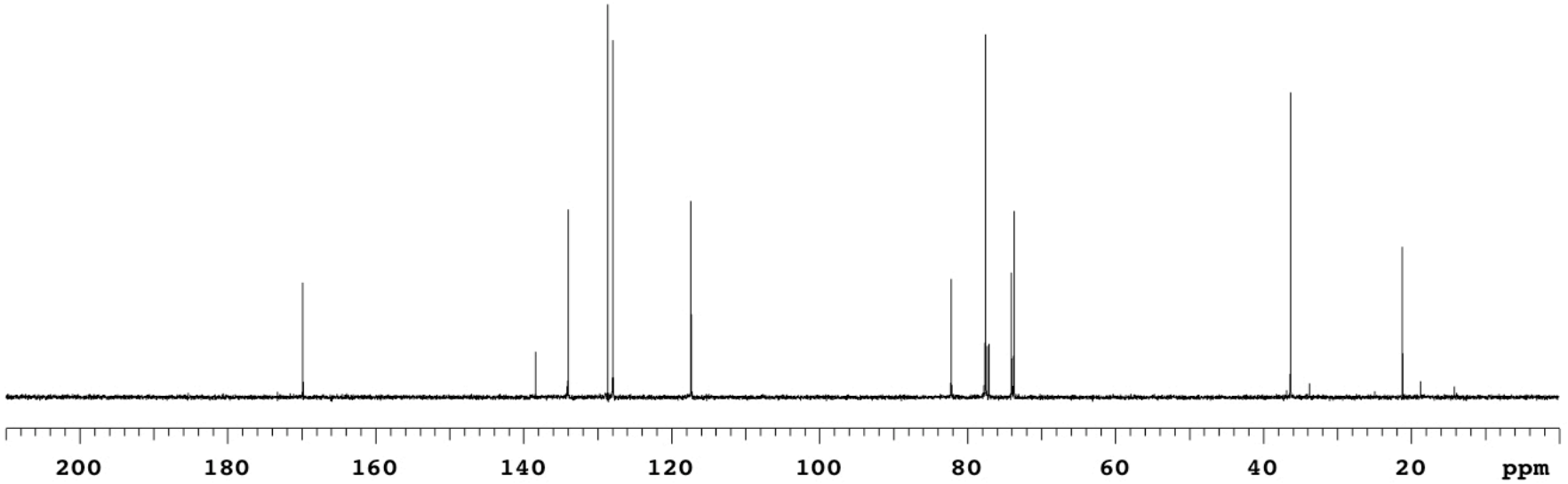

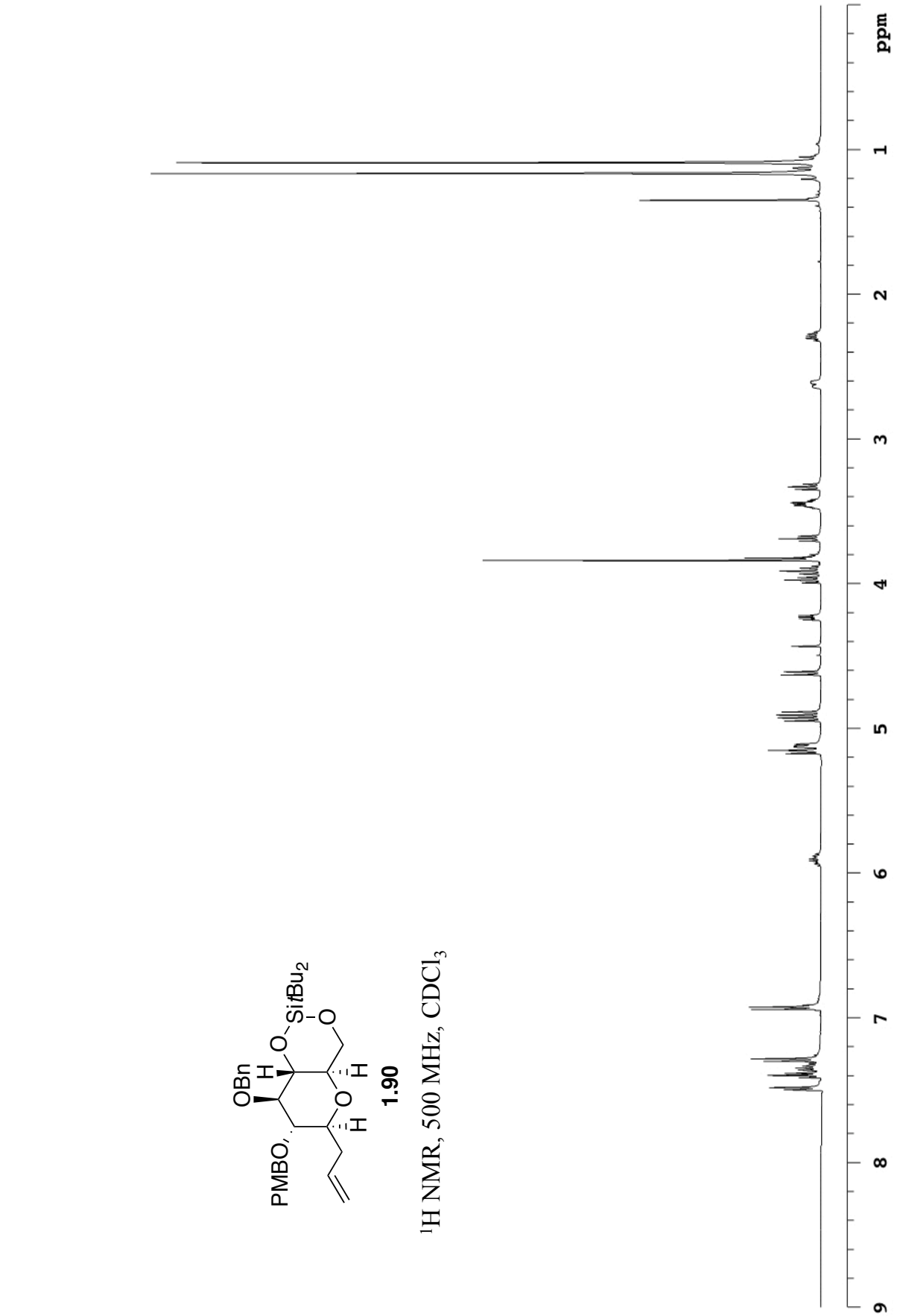

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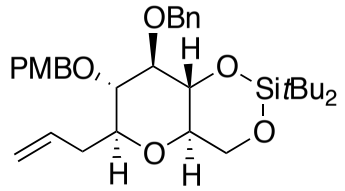

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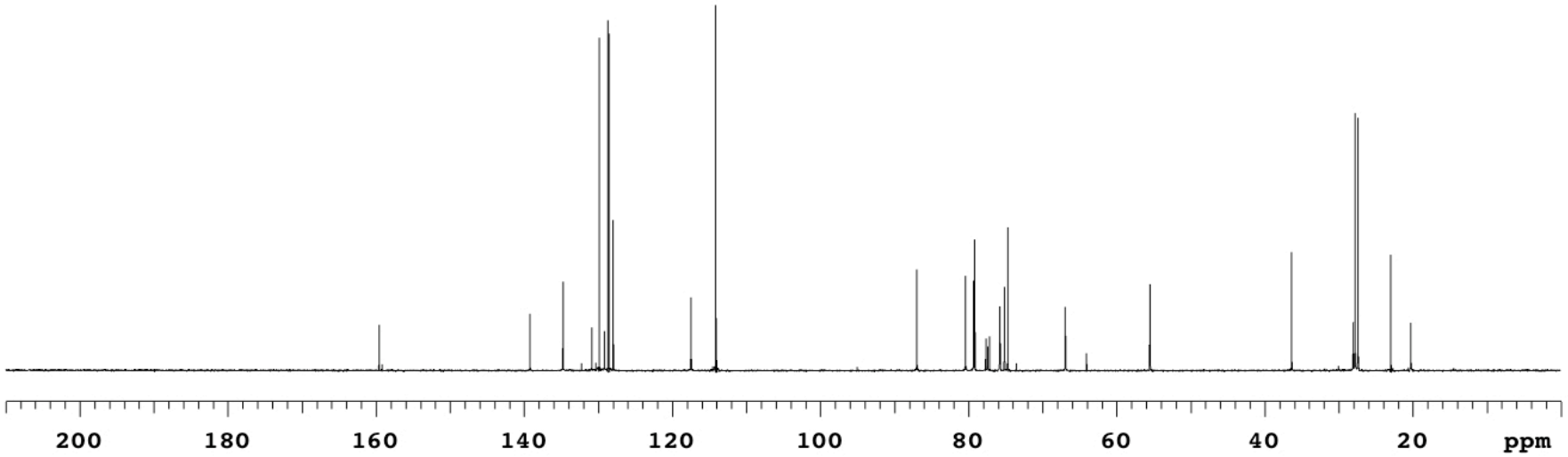
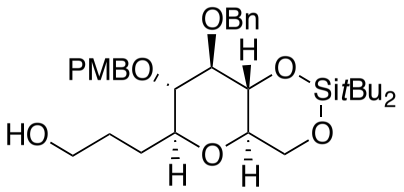
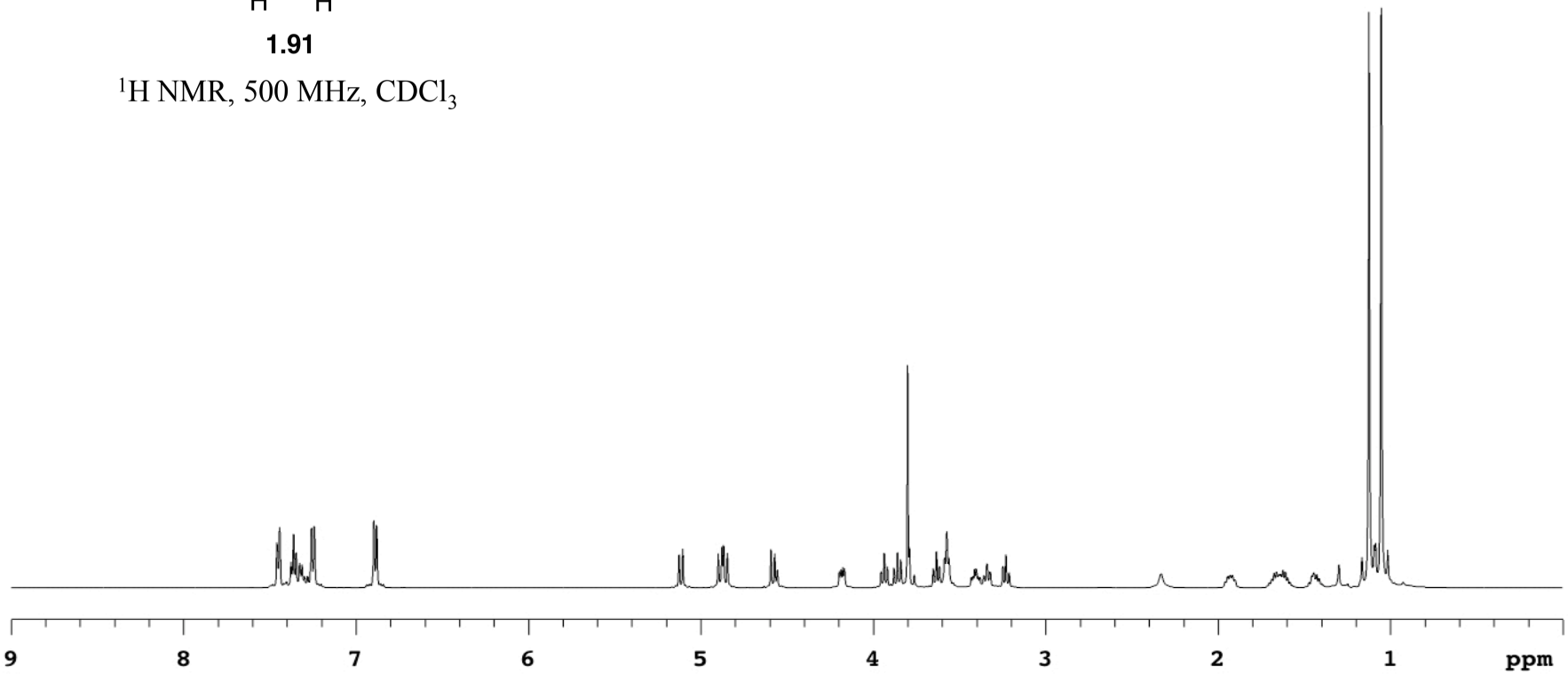
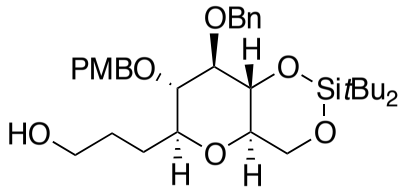




1.91

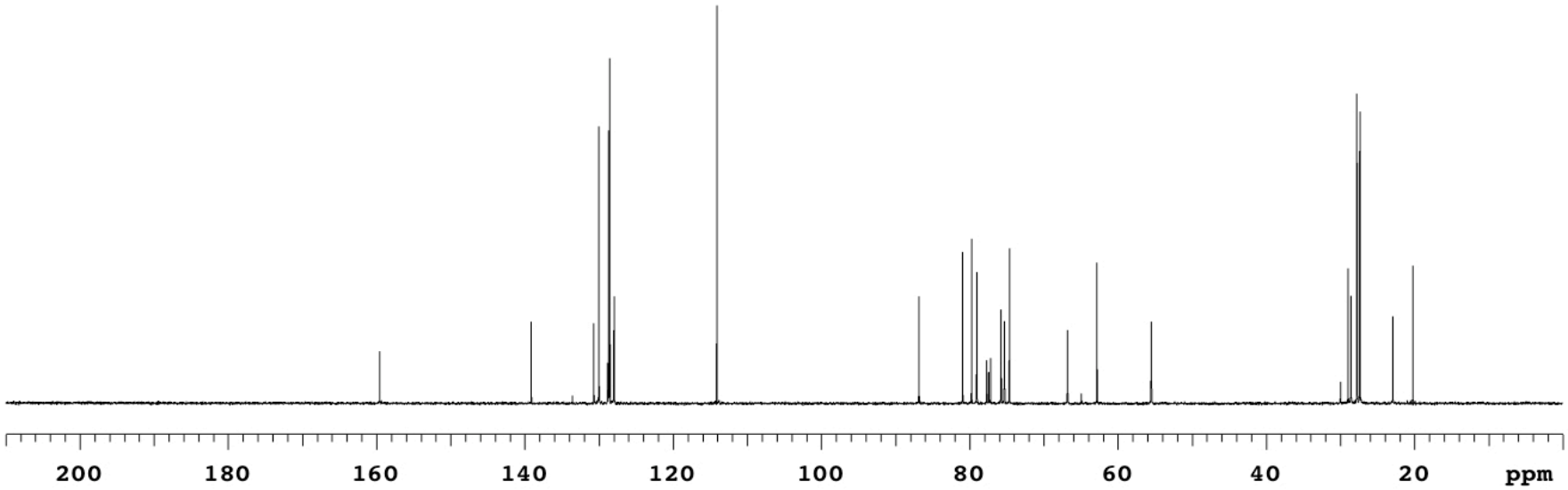
^{1}H NMR, 500 MHz, $CDCl_3$

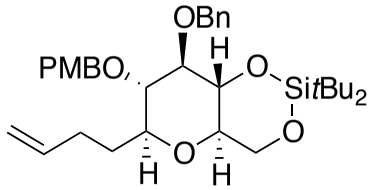




1.91

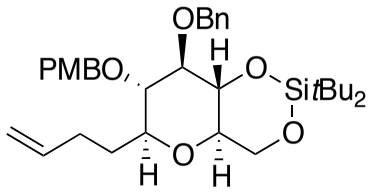
^{13}C NMR, 125 MHz, $CDCl_3$





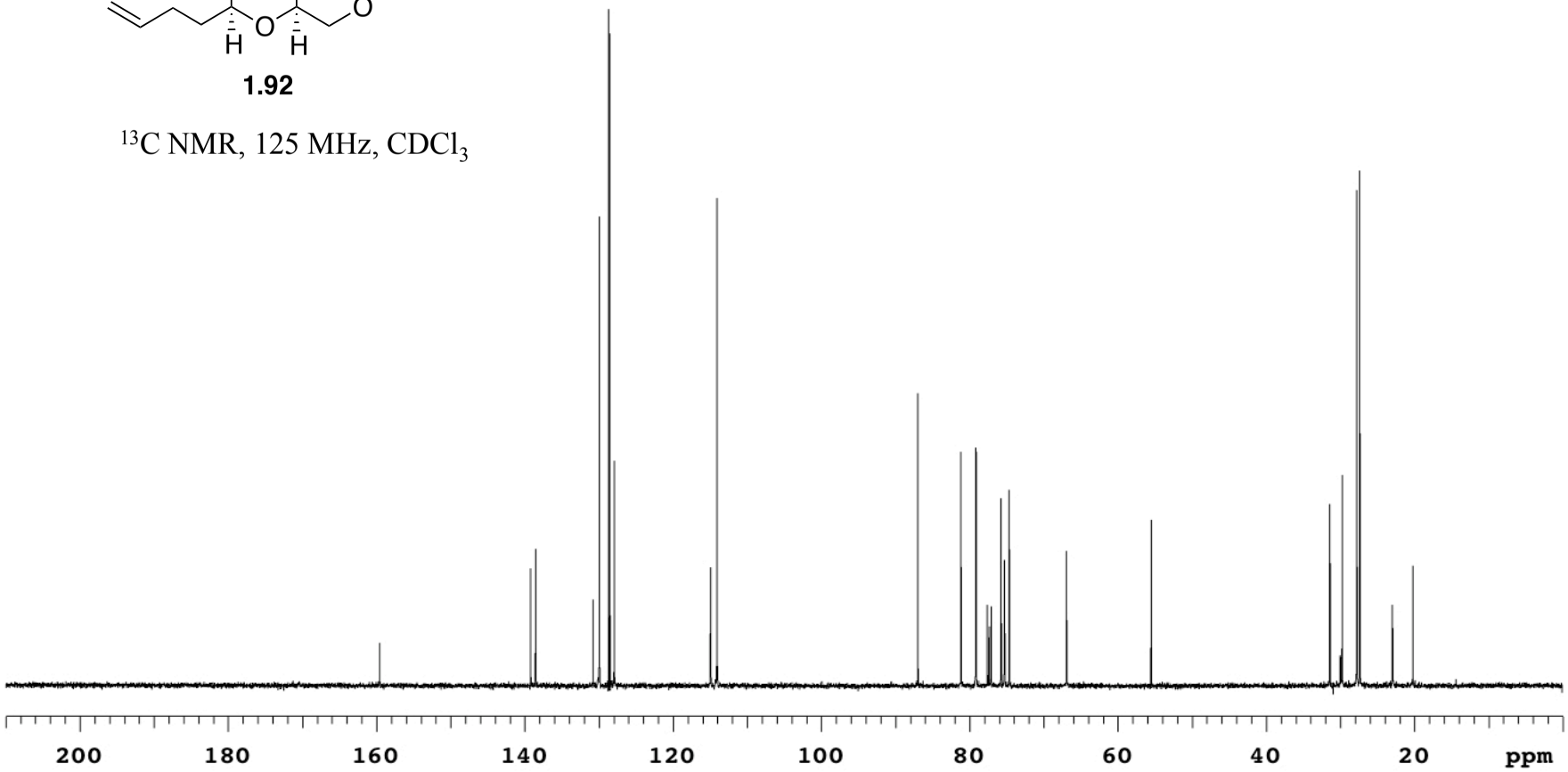
1.92

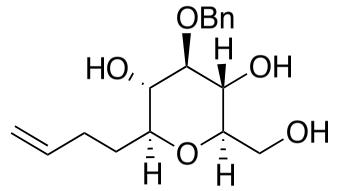
^{1}H NMR, 500 MHz, $CDCl_3$



1.92

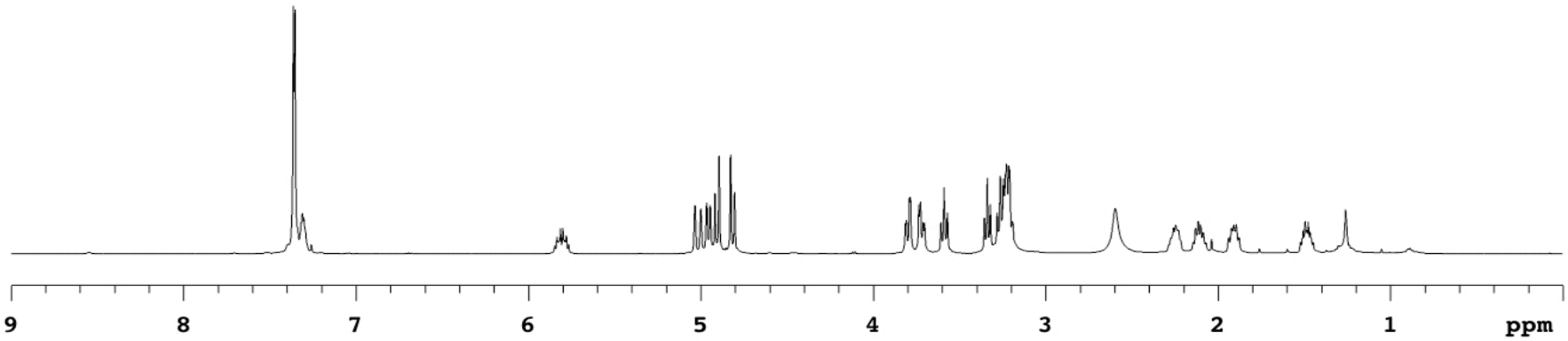
^{13}C NMR, 125 MHz, $CDCl_3$

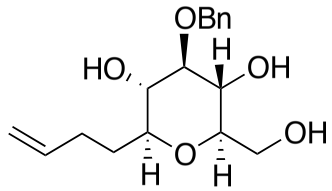




1.93

^{1}H NMR, 500 MHz, $CDCl_3$





1.93

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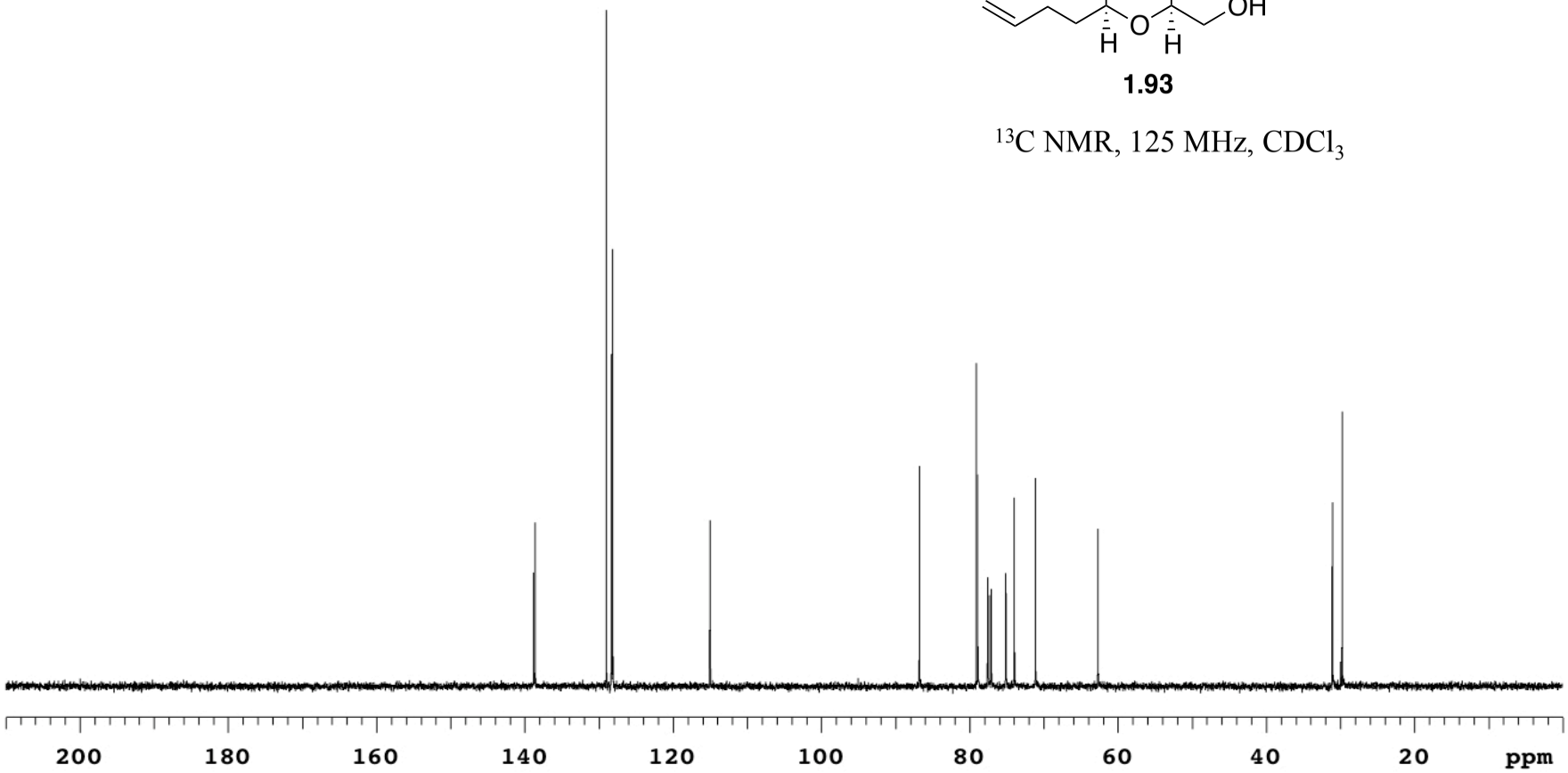

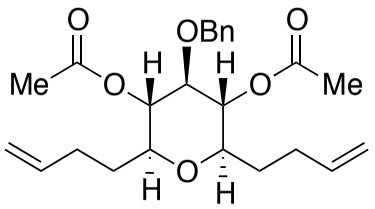

1.95

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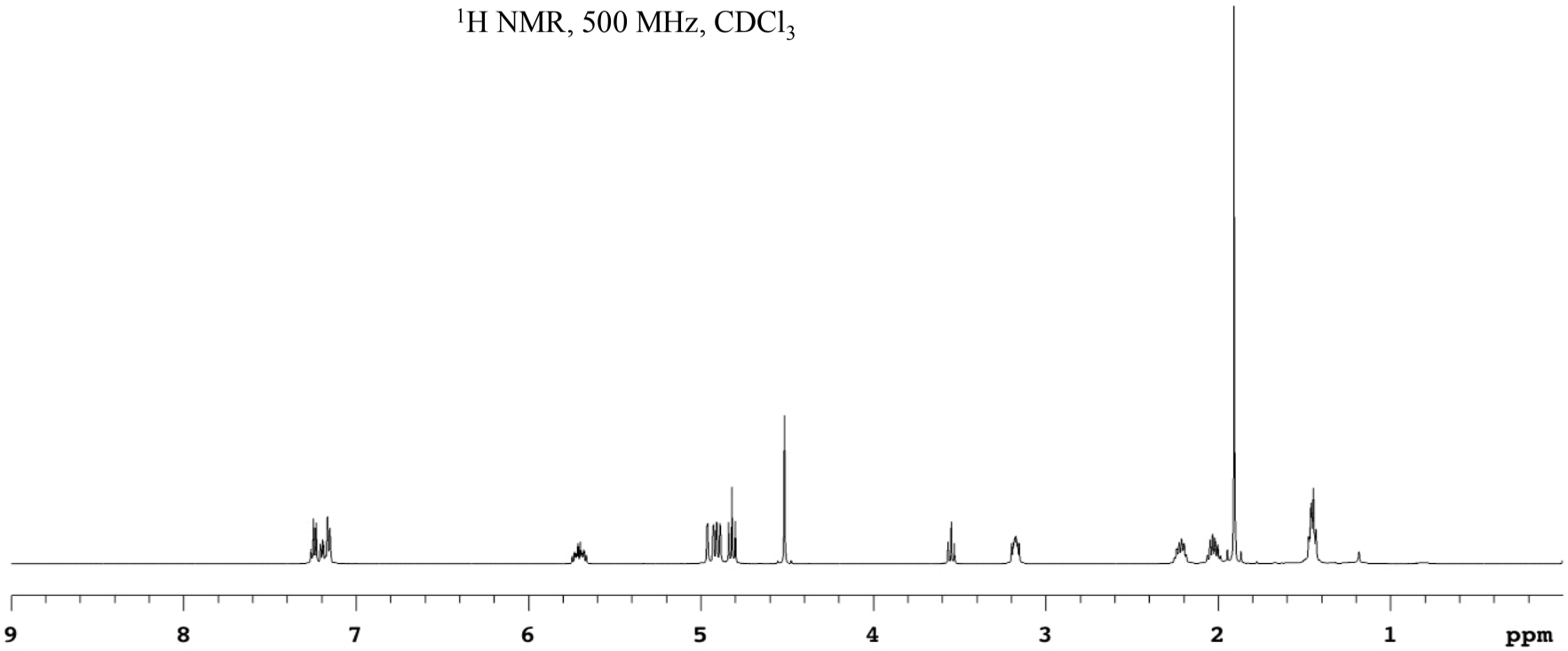
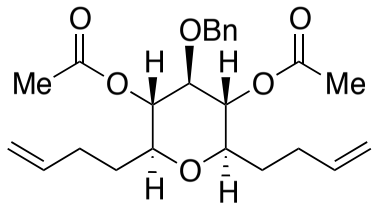
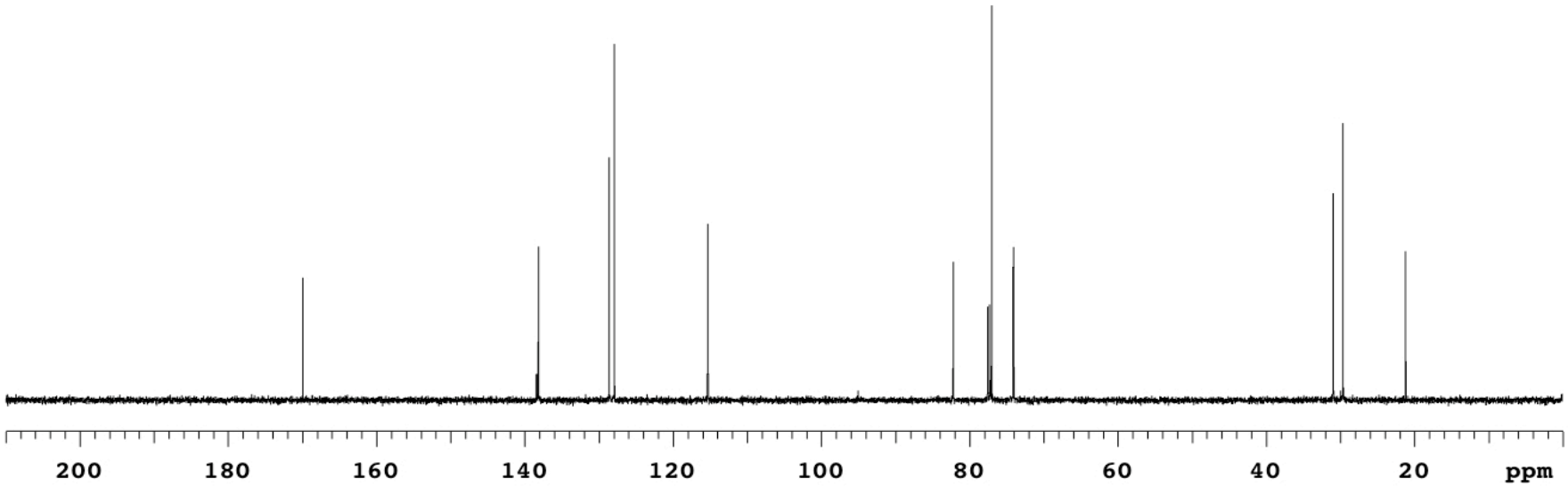
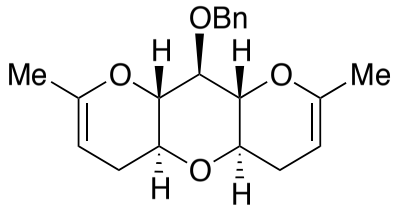




1.95

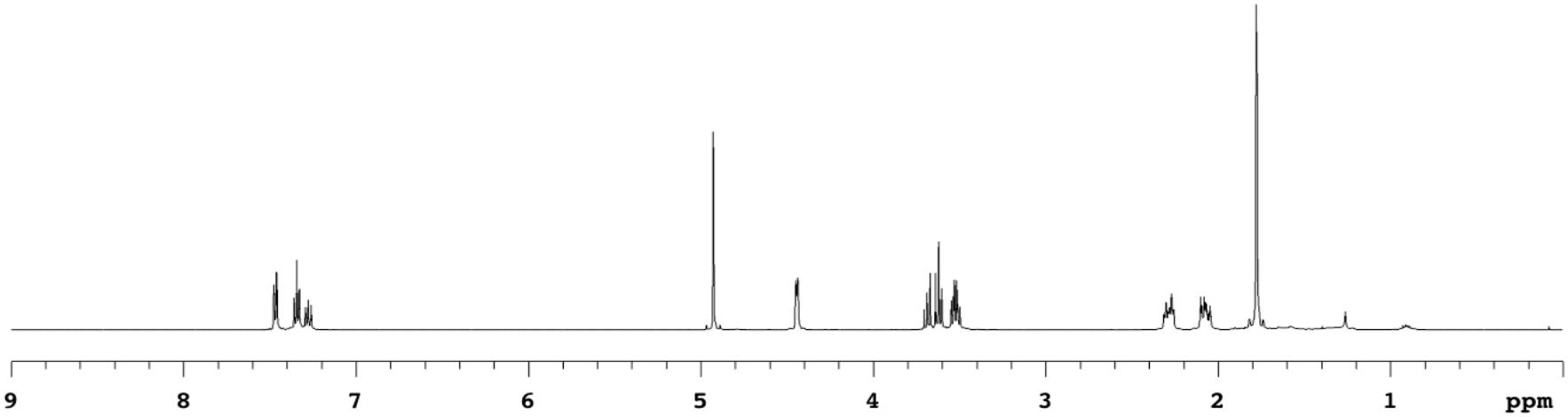
^{13}C NMR, 125 MHz, $CDCl_3$

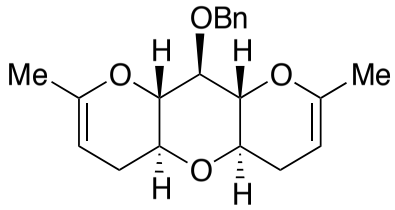




1.96

^{1}H NMR, 500 MHz, $CDCl_3$





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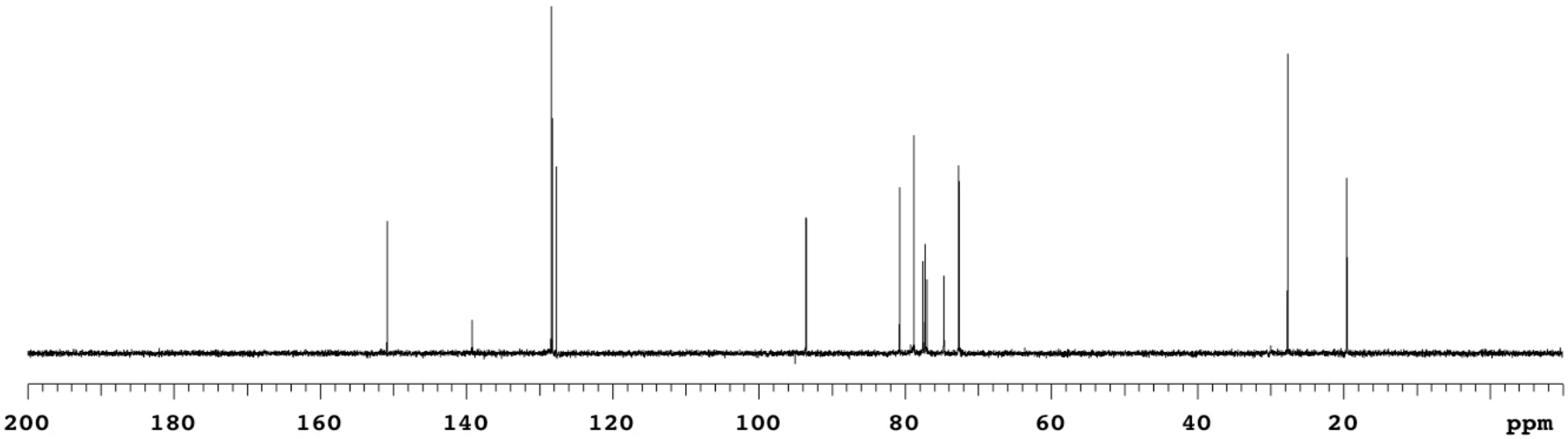
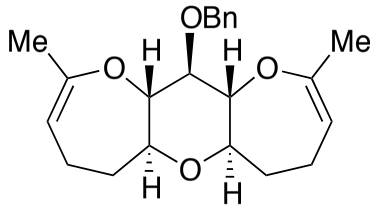
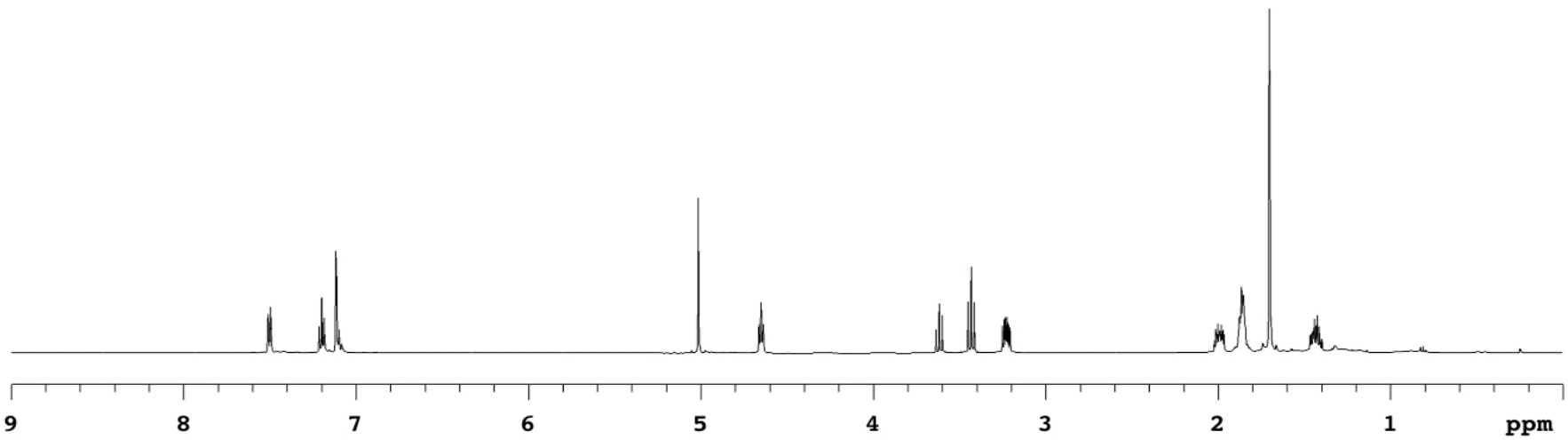
^{13}C NMR, 125 MHz, $CDCl_3$

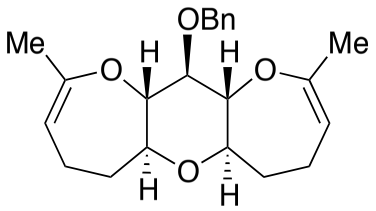




1.97

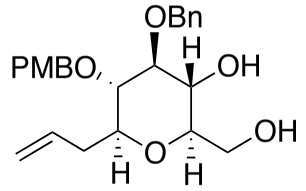
^{1}H NMR, 500 MHz, C_6D_6





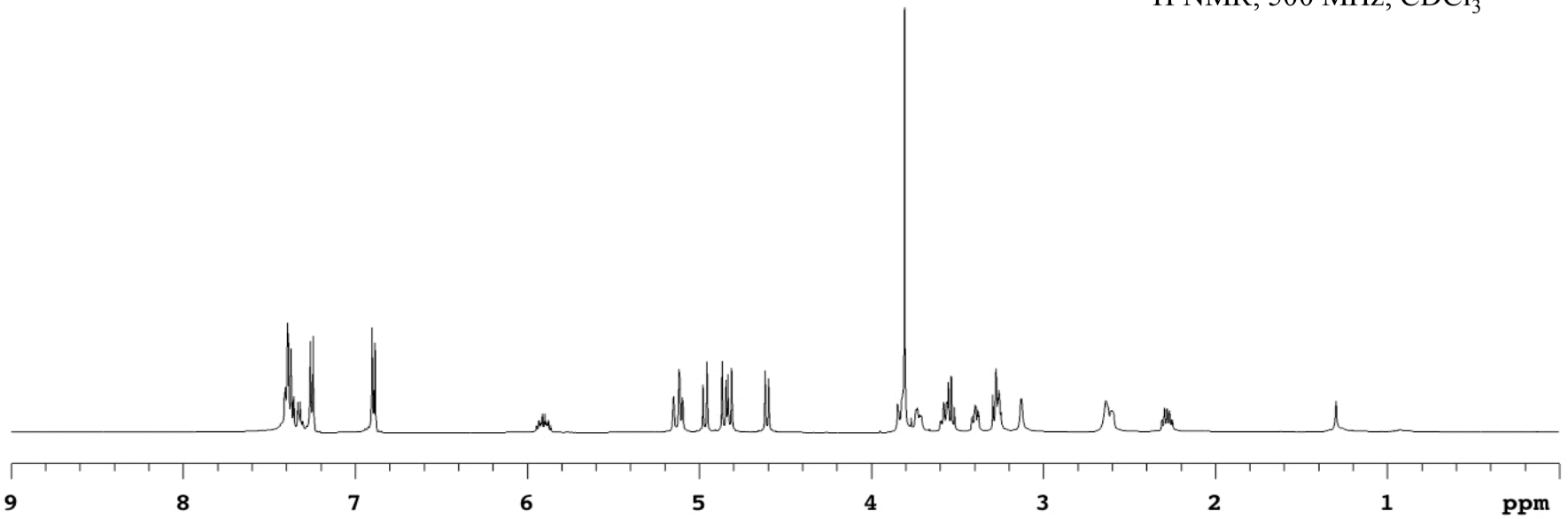
1.97

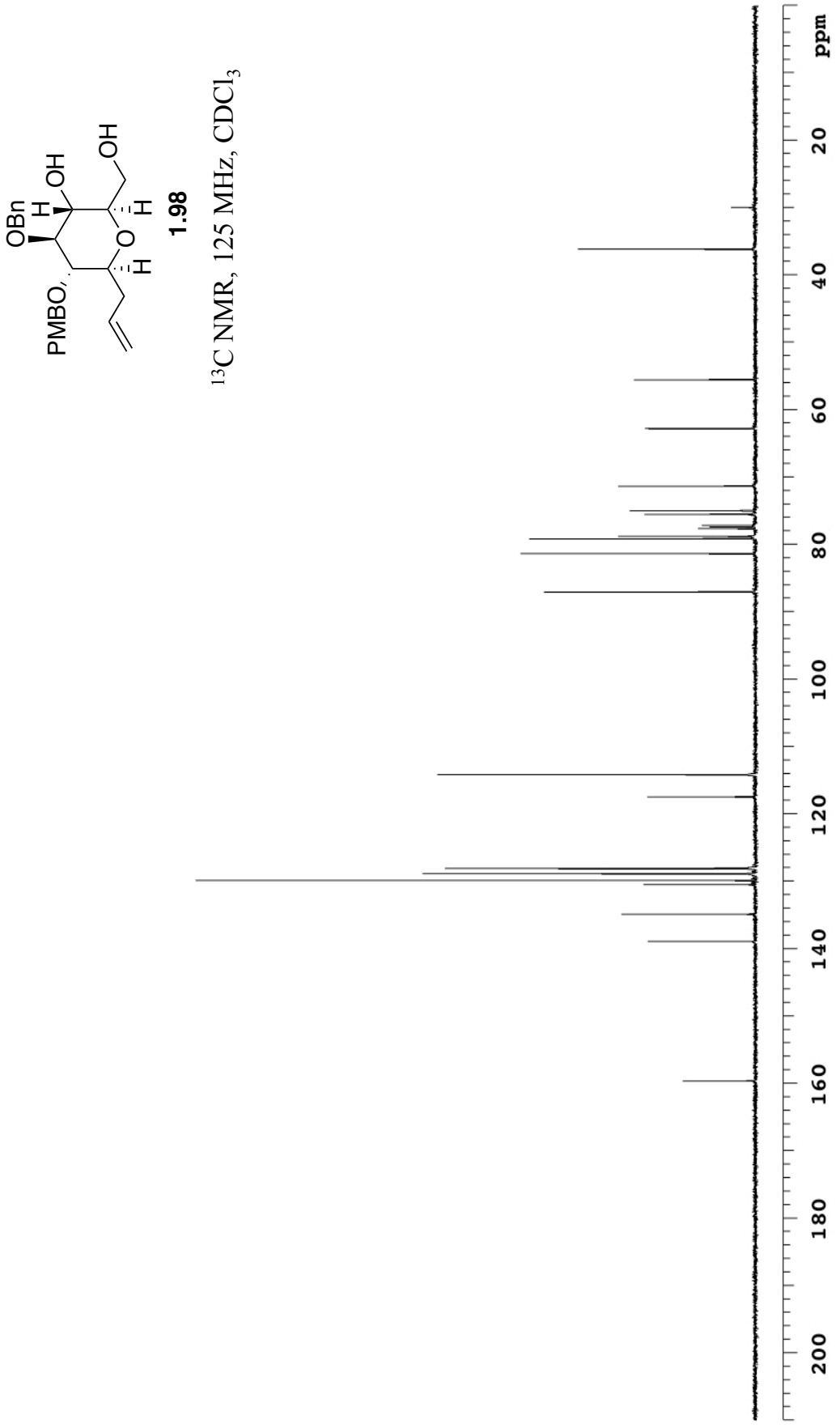
^{13}C NMR, 125 MHz, C_6D_6

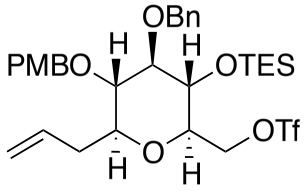


1.98

^{1}H NMR, 500 MHz, $CDCl_3$

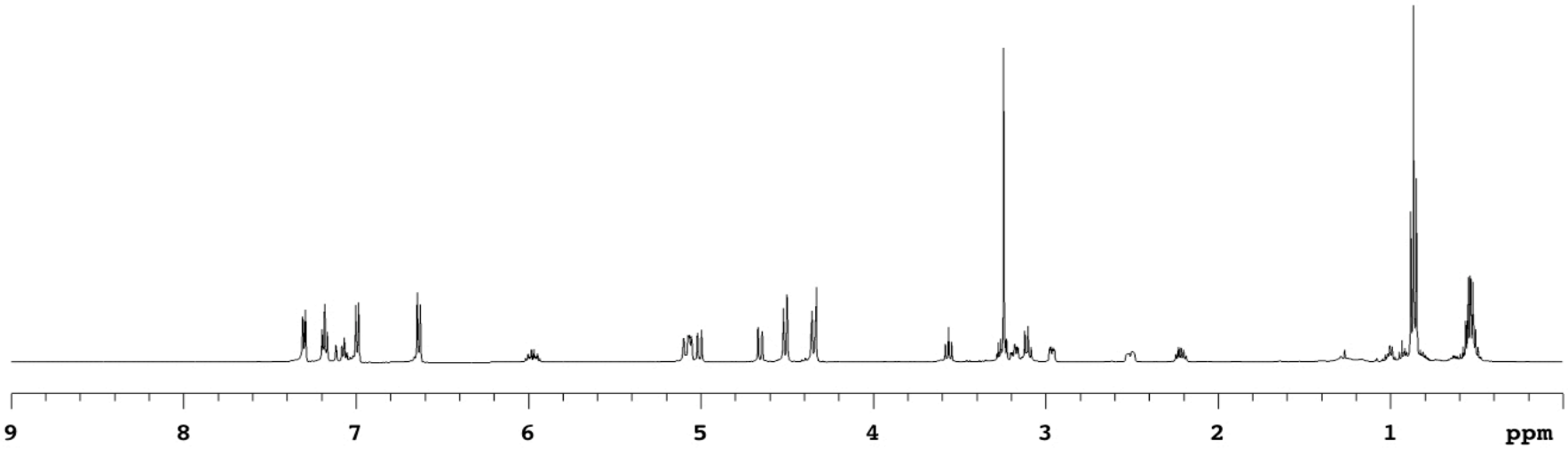


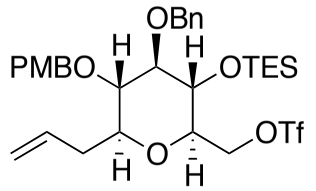

OBn
H
OH
PMBO
O
H
H
OH
1.98
^{13}C NMR, 125 MHz, $CDCl_3$
200
180
160
140
120
100
80
60
40
20
ppm



1.99

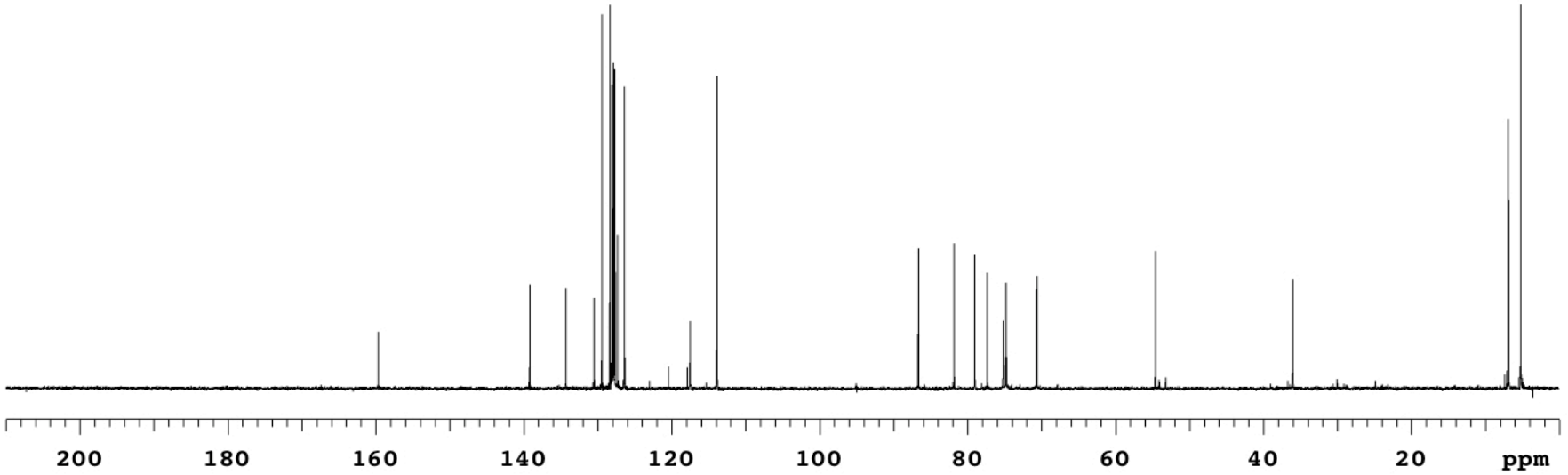
^{1}H NMR, 500 MHz, C_6D_6

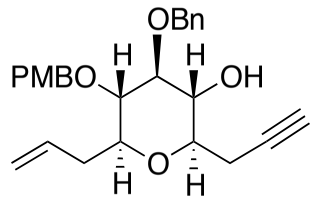




1.99

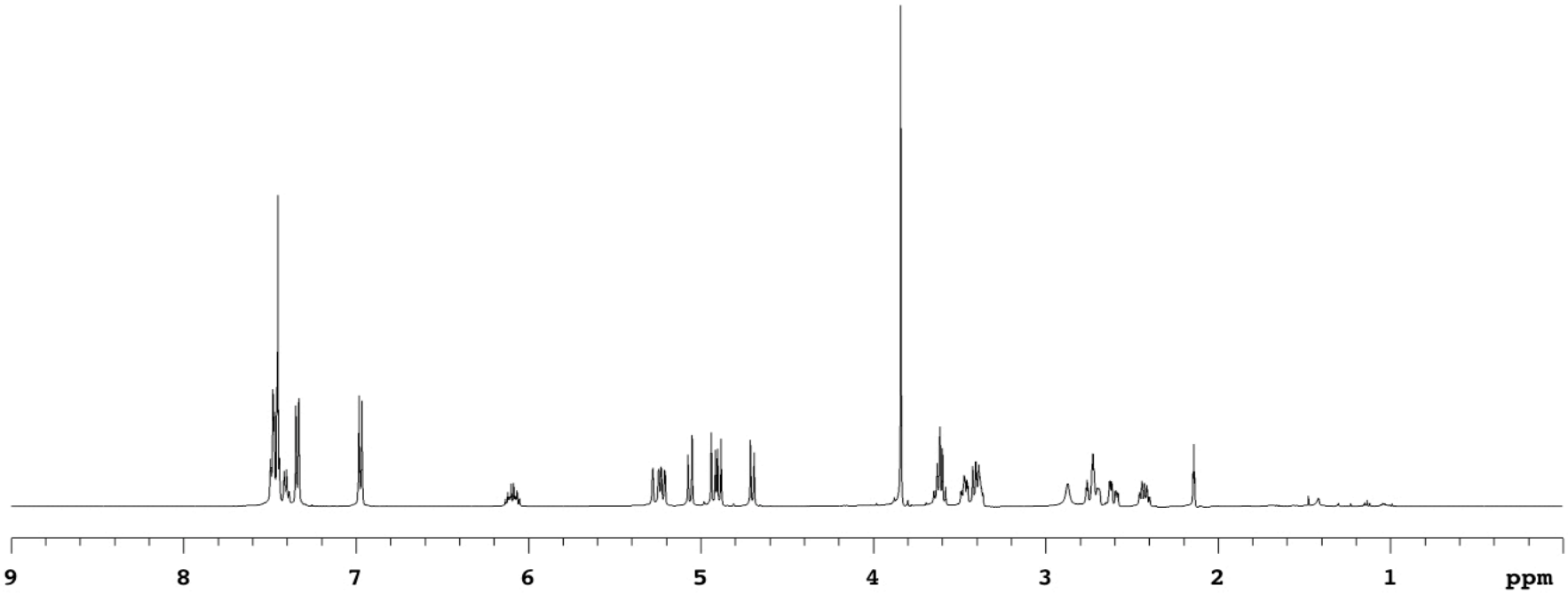
^{13}C NMR, 125 MHz, C_6D_6

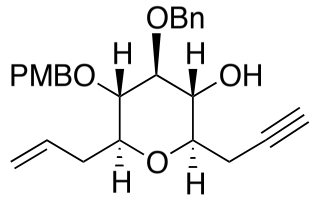




1.100

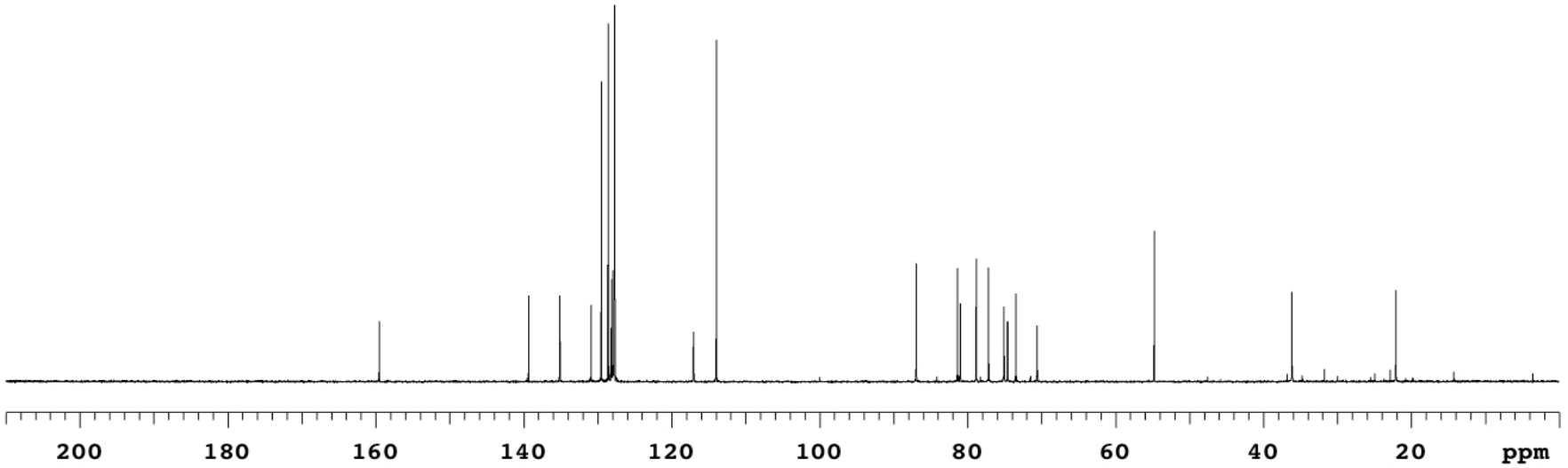
^{1}H NMR, 500 MHz, $CDCl_3$

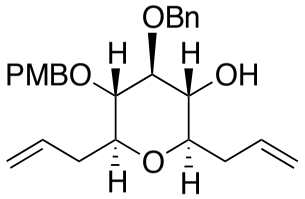




1.100

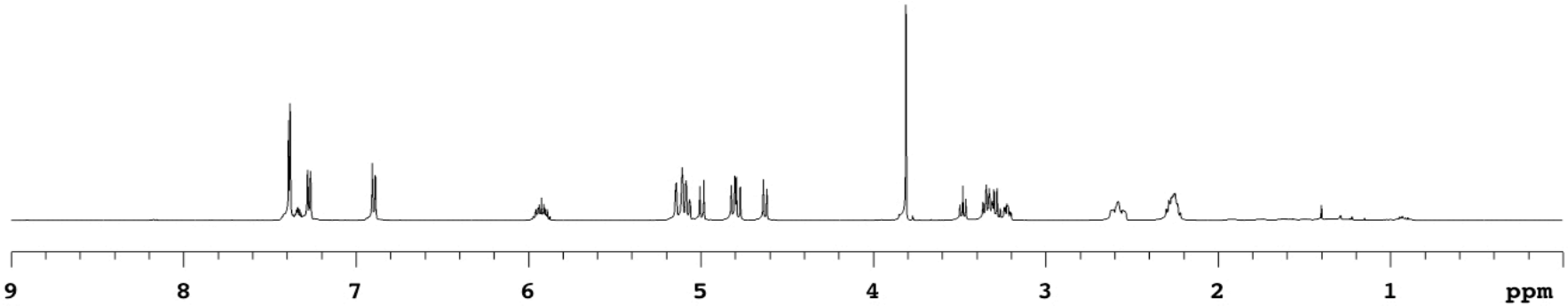
^{13}C NMR, 125 MHz, C_6D_6

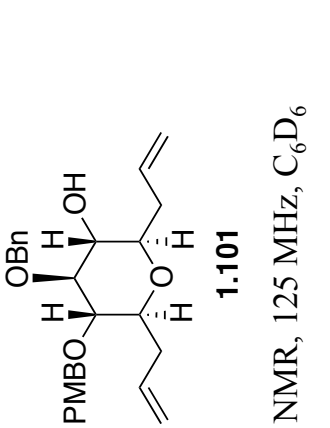




1.101

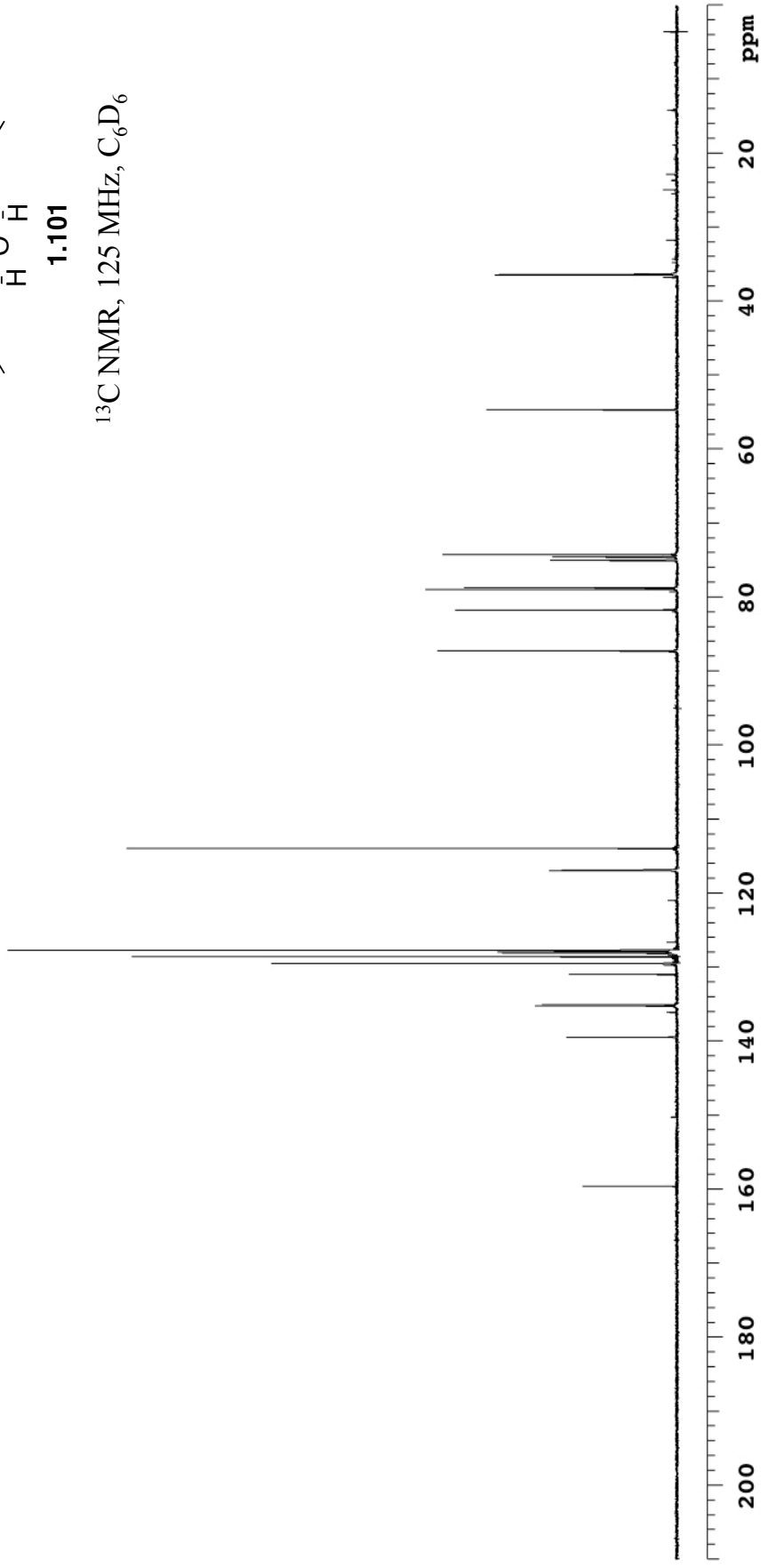
^{1}H NMR, 500 MHz, C_6D_6

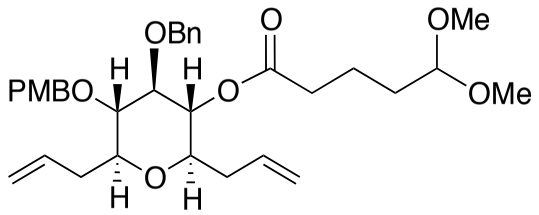




1.101

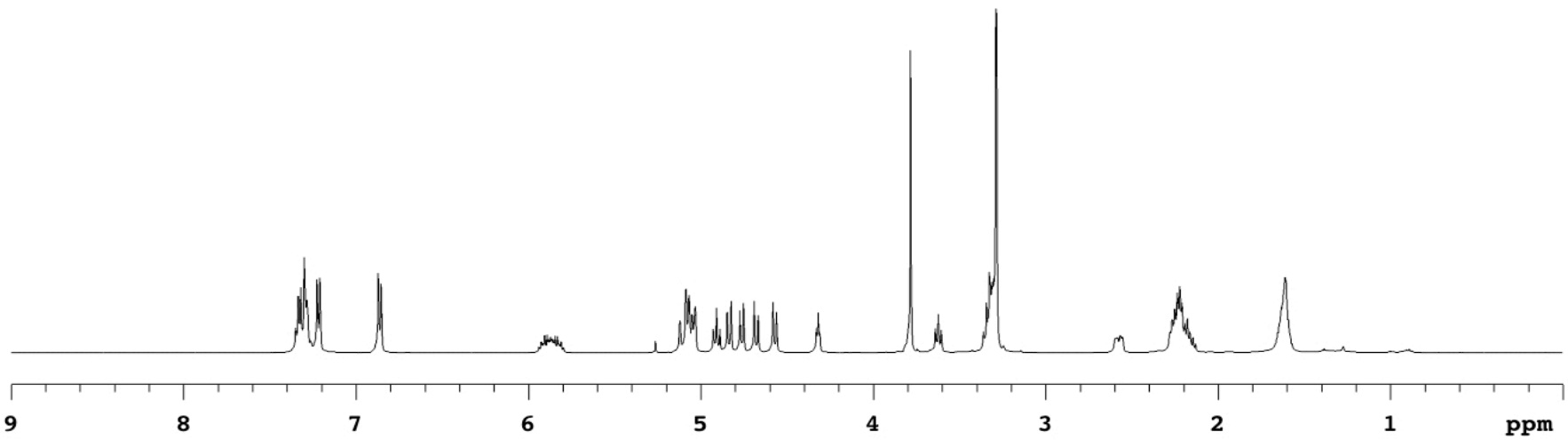
^{13}C NMR, 125 MHz, C_6D_6

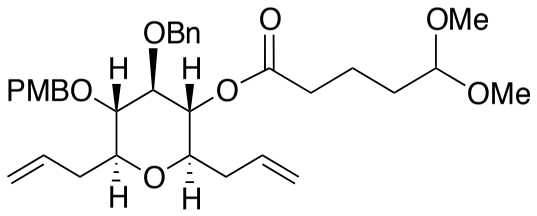




1.103

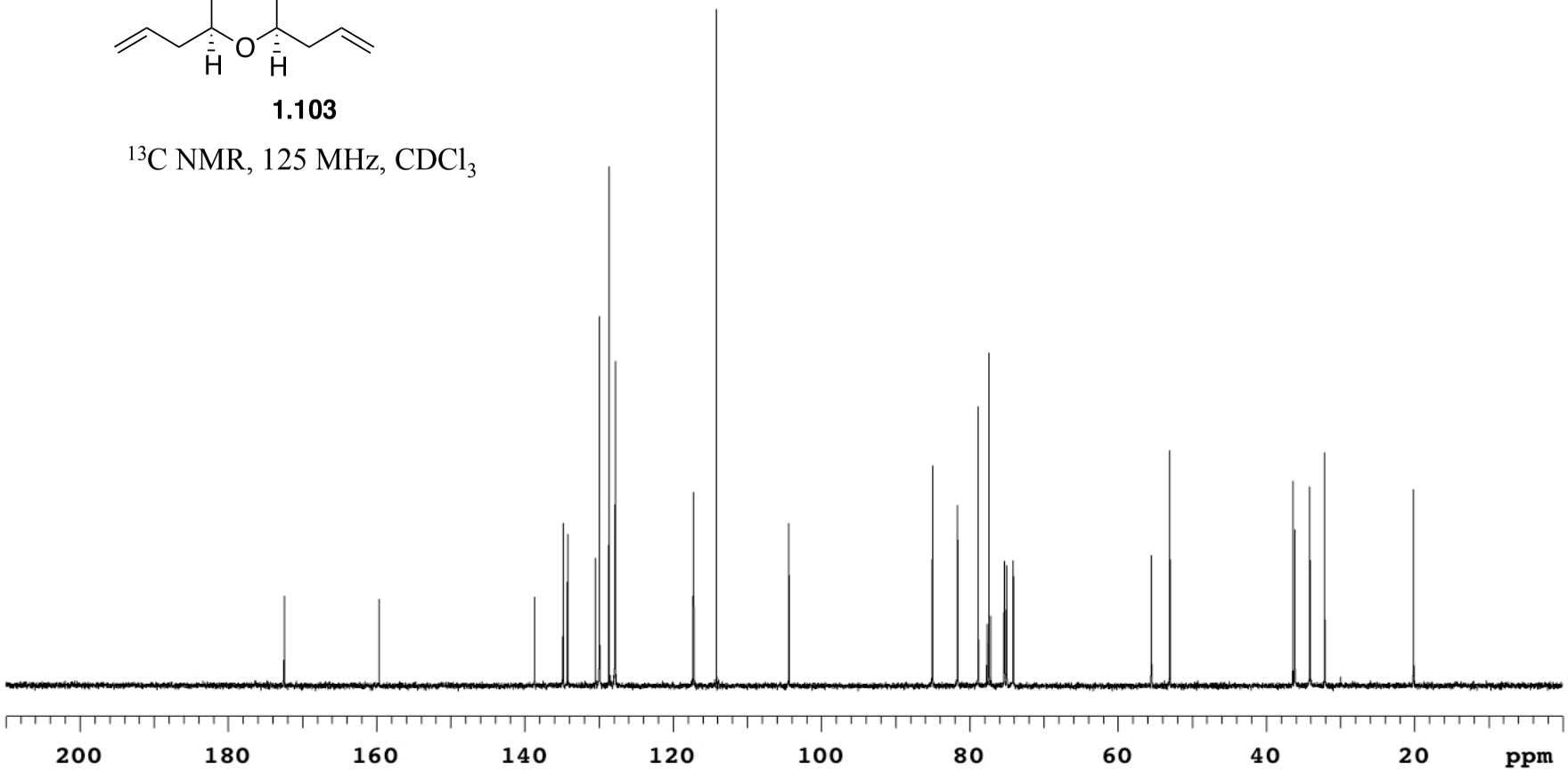
^{1}H NMR, 500 MHz, $CDCl_3$

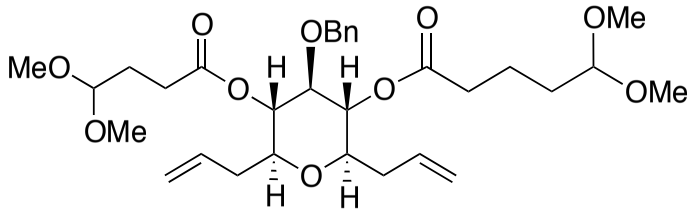




1.103

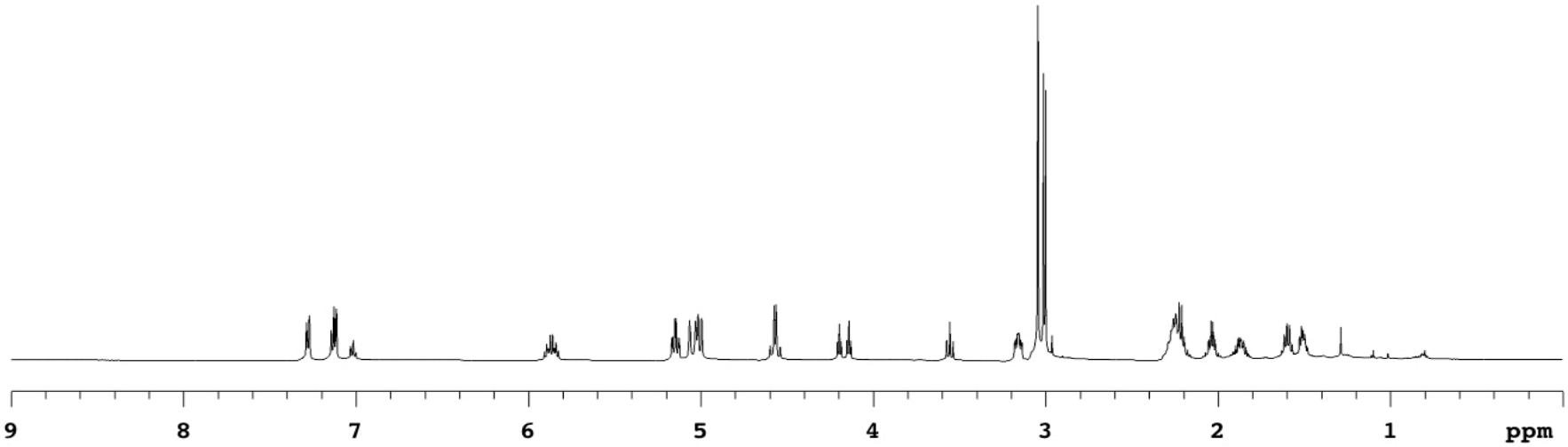
^{13}C NMR, 125 MHz, $CDCl_3$

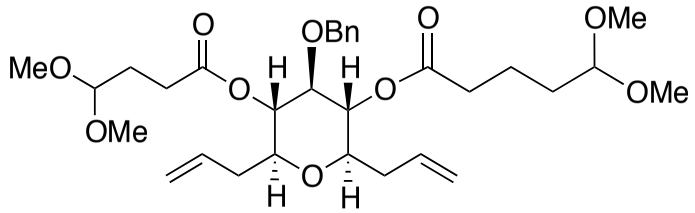




1.105

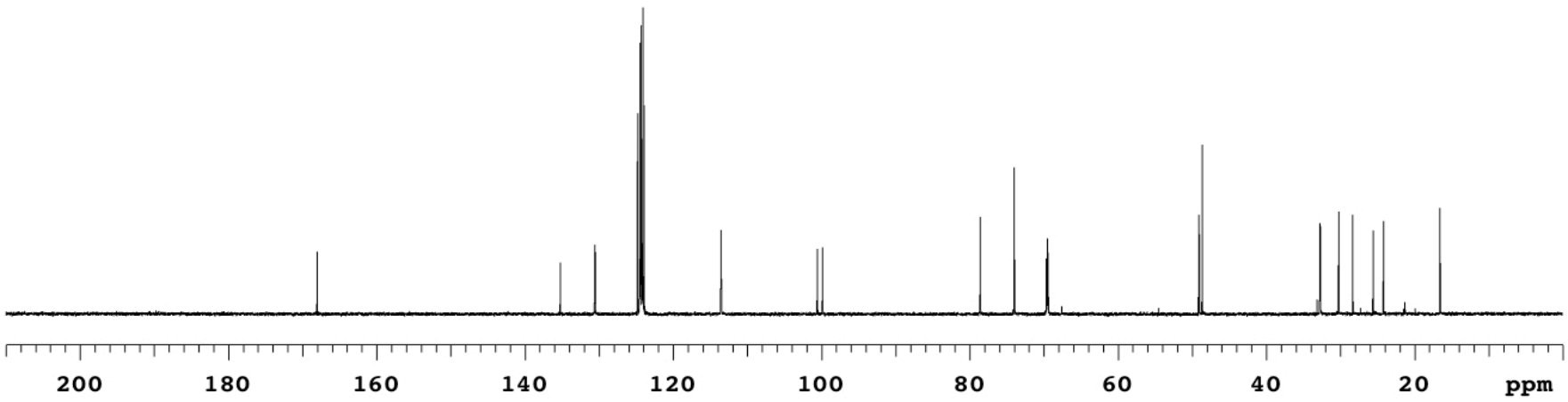
^{1}H NMR, 500 MHz, C_6D_6

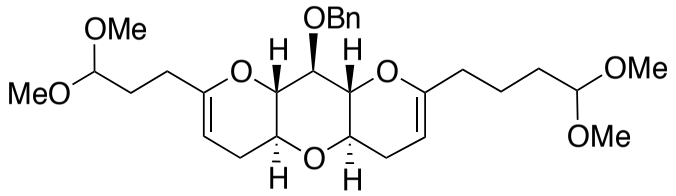




1.105

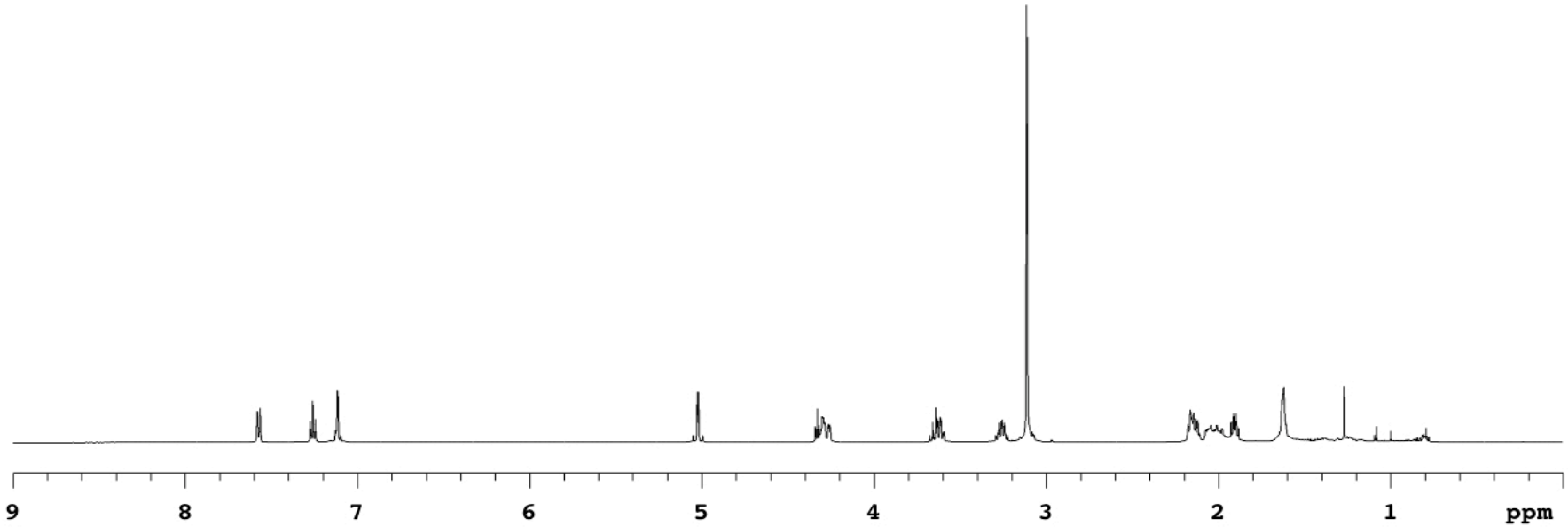
^{13}C NMR, 125 MHz, C_6D_6

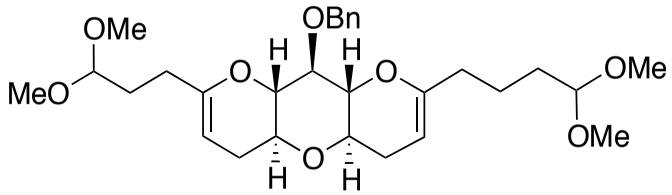




1.106

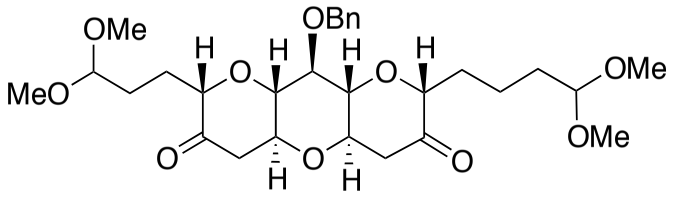
^{1}H NMR, 500 MHz, C_6D_6





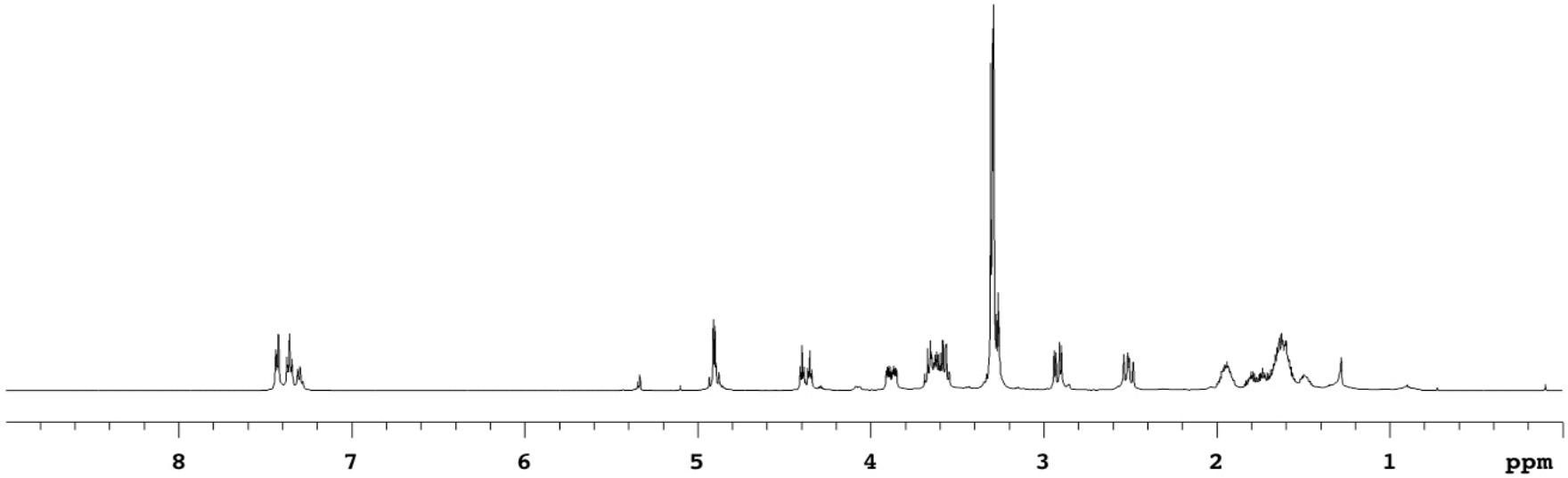
1.106

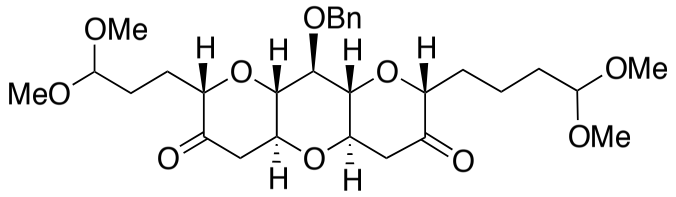
^{13}C NMR, 125 MHz, C_6D_6



1.108

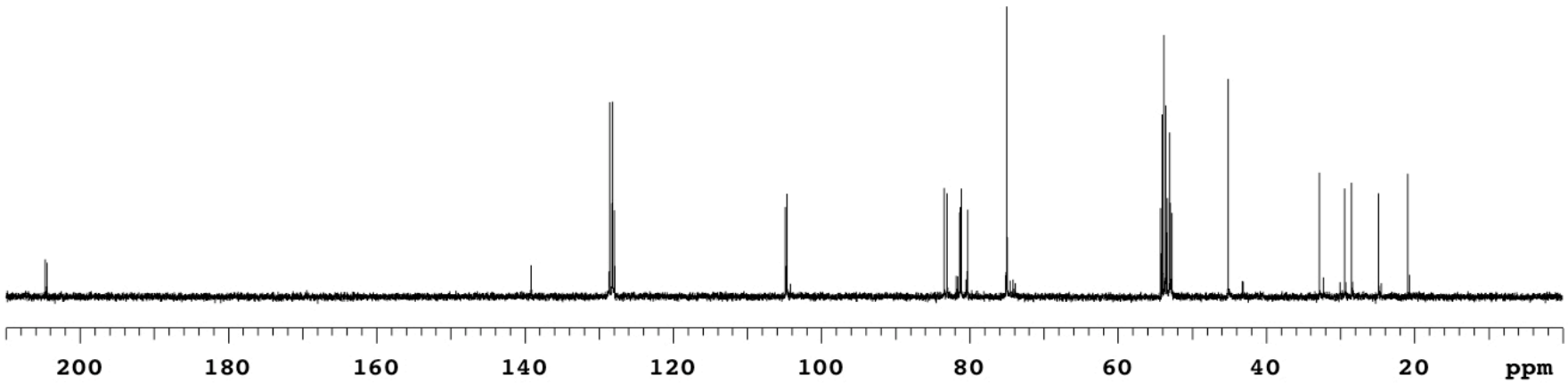
^{1}H NMR, 500 MHz, CD_2Cl_2

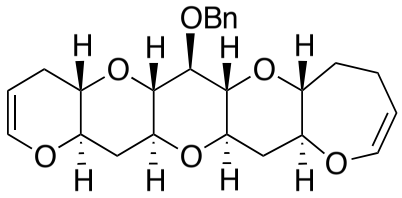




1.108

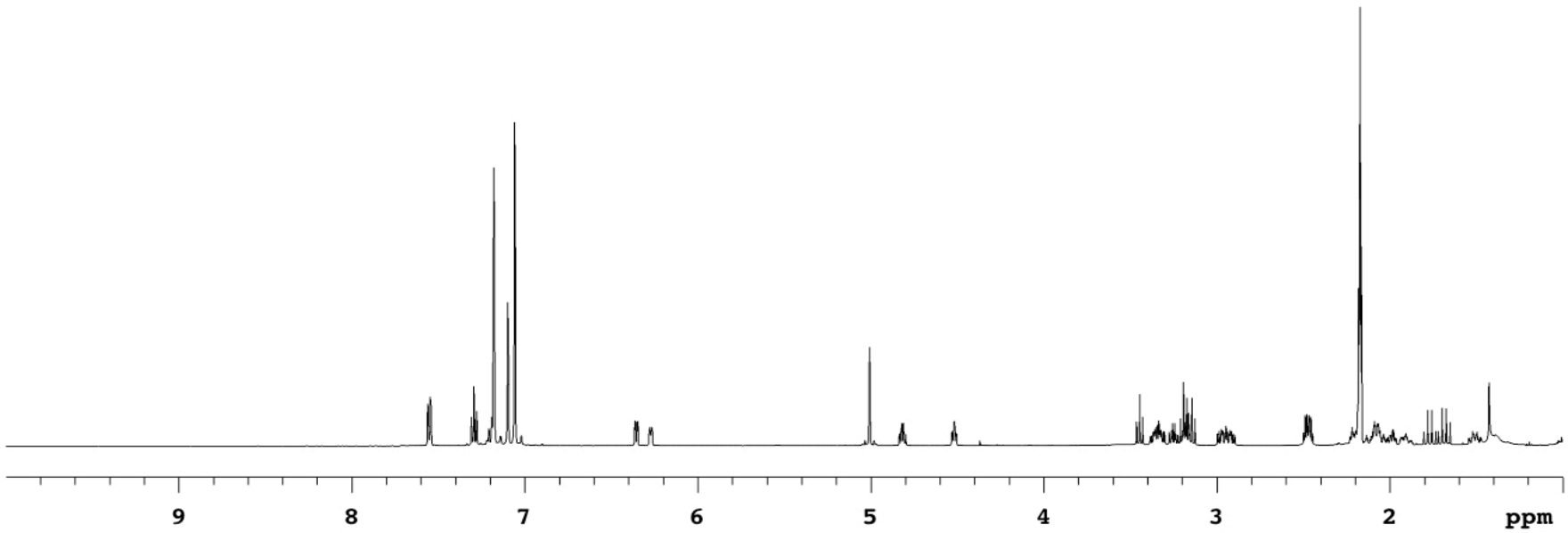
^{13}C NMR, 125 MHz, CD_2Cl_2

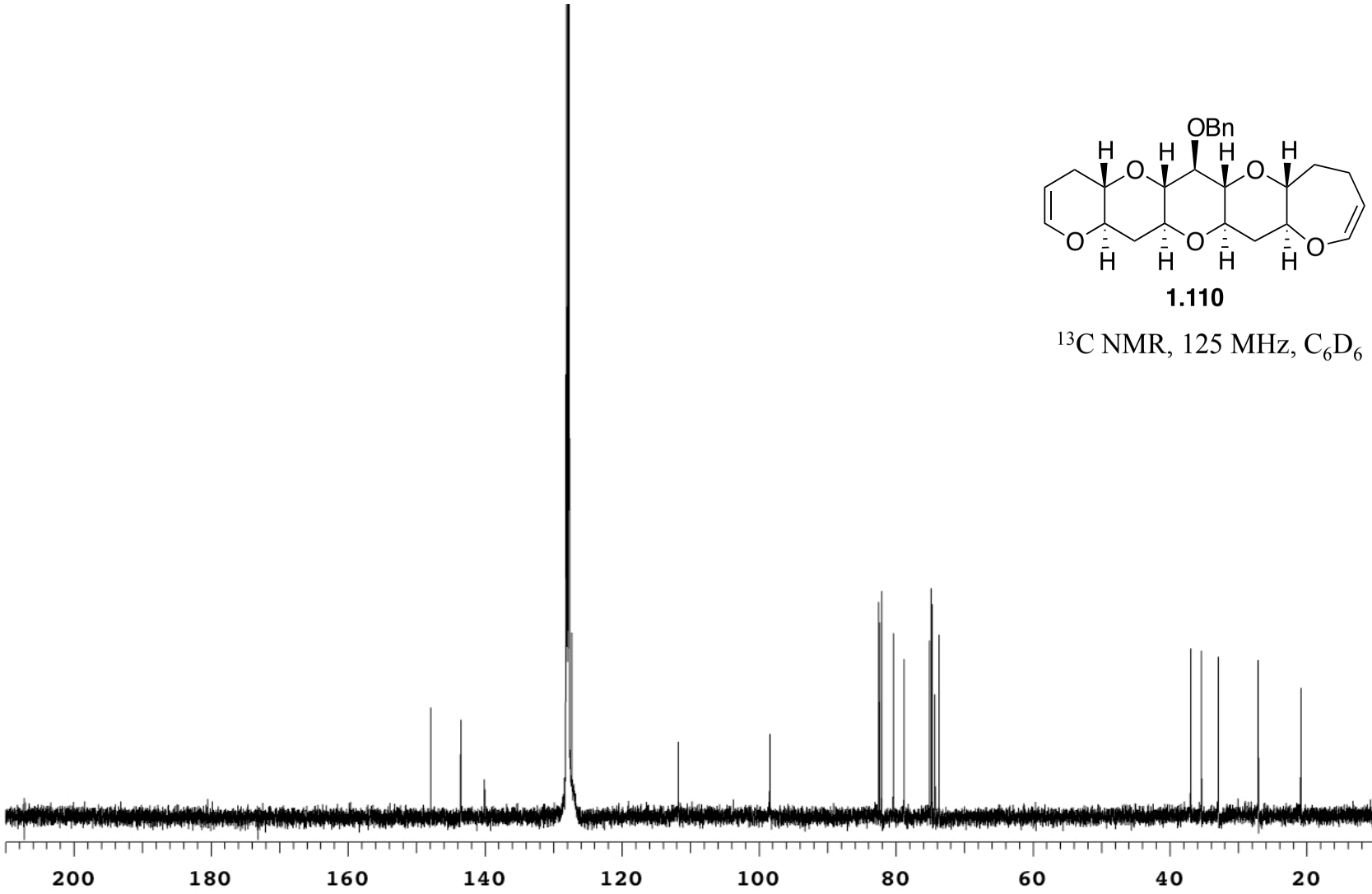




1.110

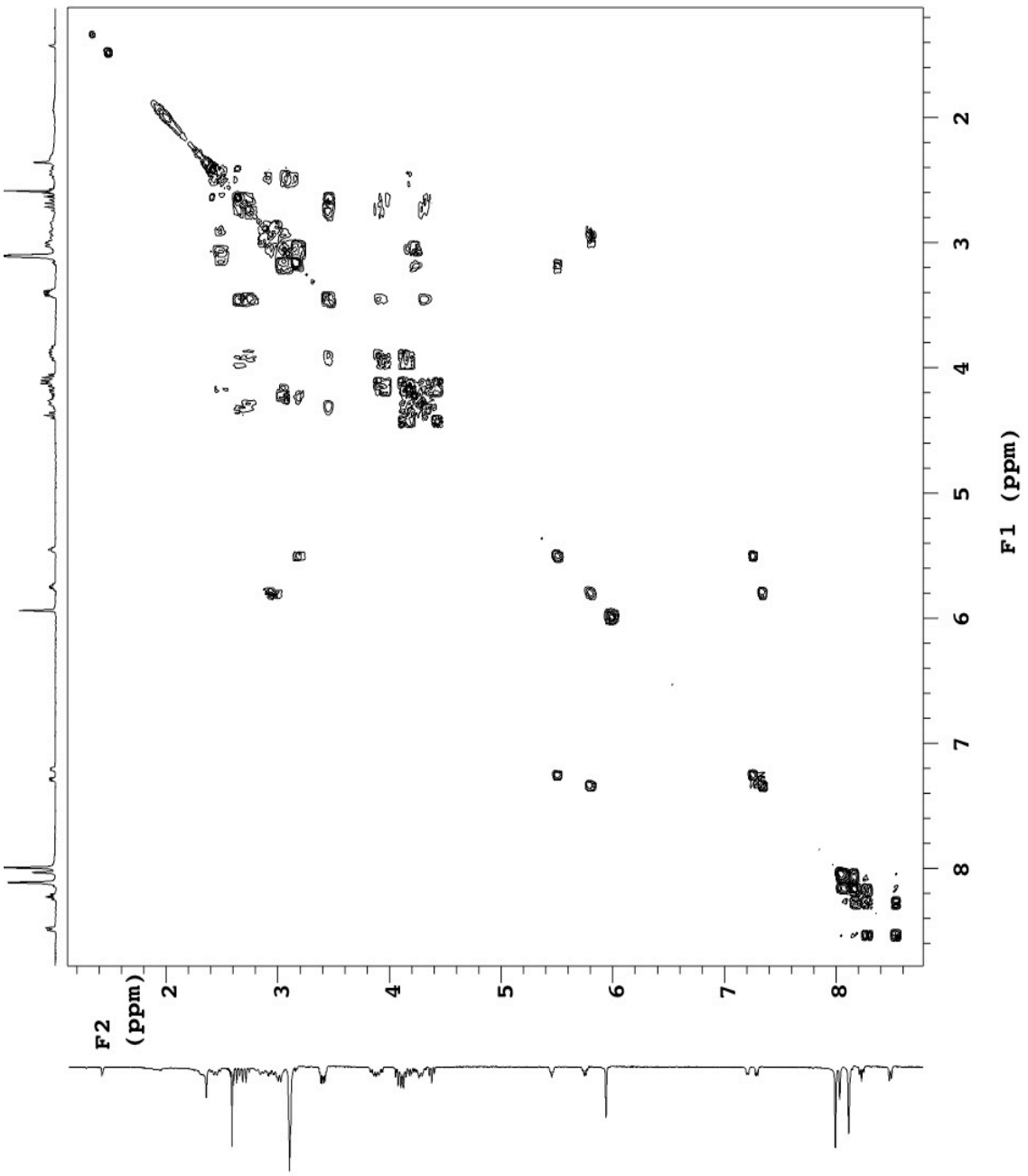
^{1}H NMR, 500 MHz, C_7H_8

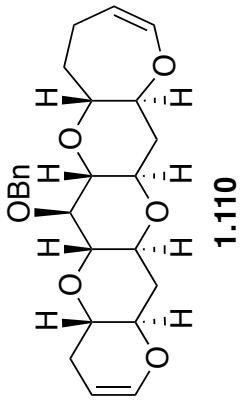




1.110

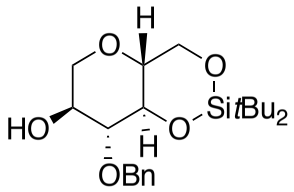
^{13}C NMR, 125 MHz, C_6D_6





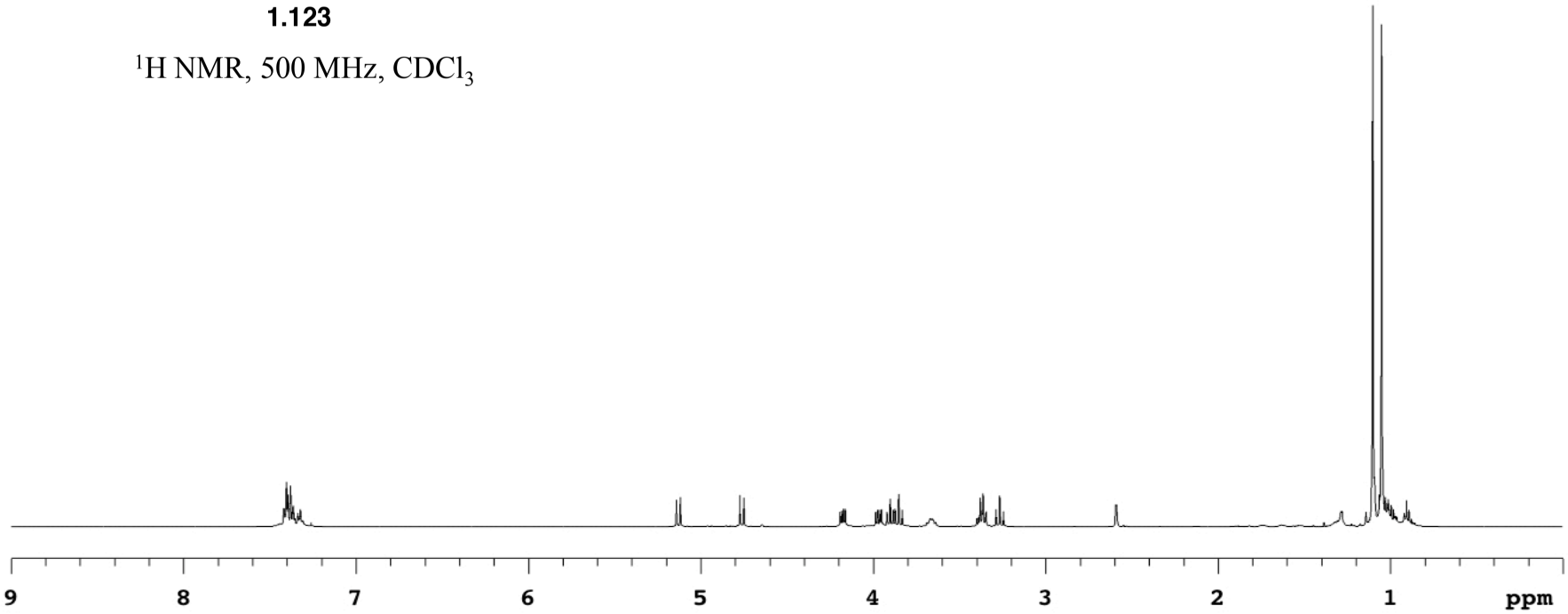
1.110

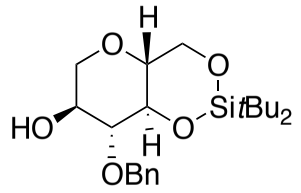
^{1}H NMR, 500 MHz, C_7H_8



1.123

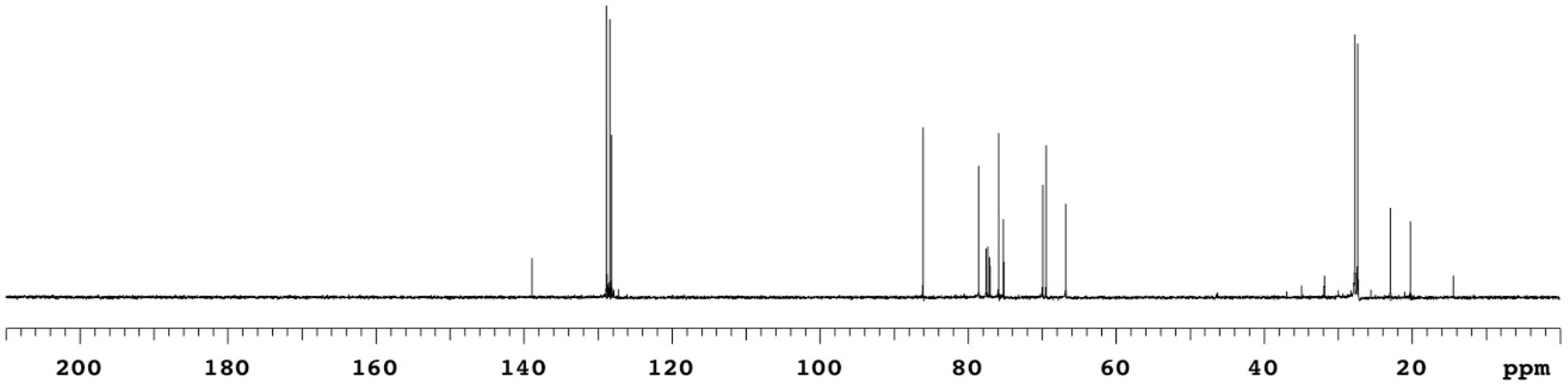
^{1}H NMR, 500 MHz, $CDCl_3$

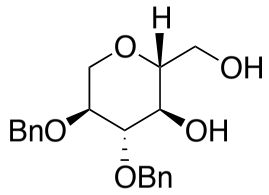




1.123

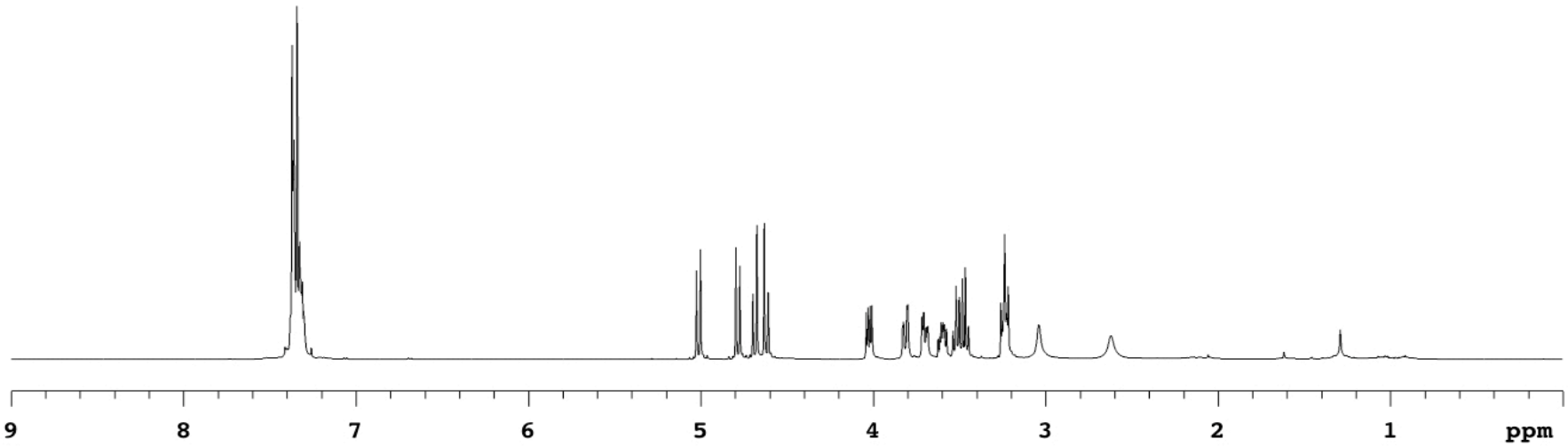
^{13}C NMR, 125 MHz, $CDCl_3$

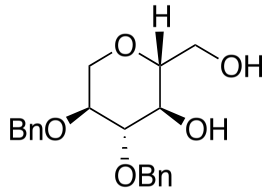




1.124

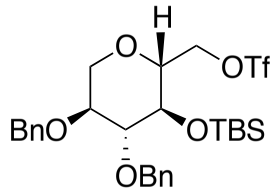
^{1}H NMR, 500 MHz, $CDCl_3$





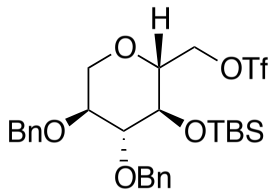
1.124

^{13}C NMR, 125 MHz, $CDCl_3$



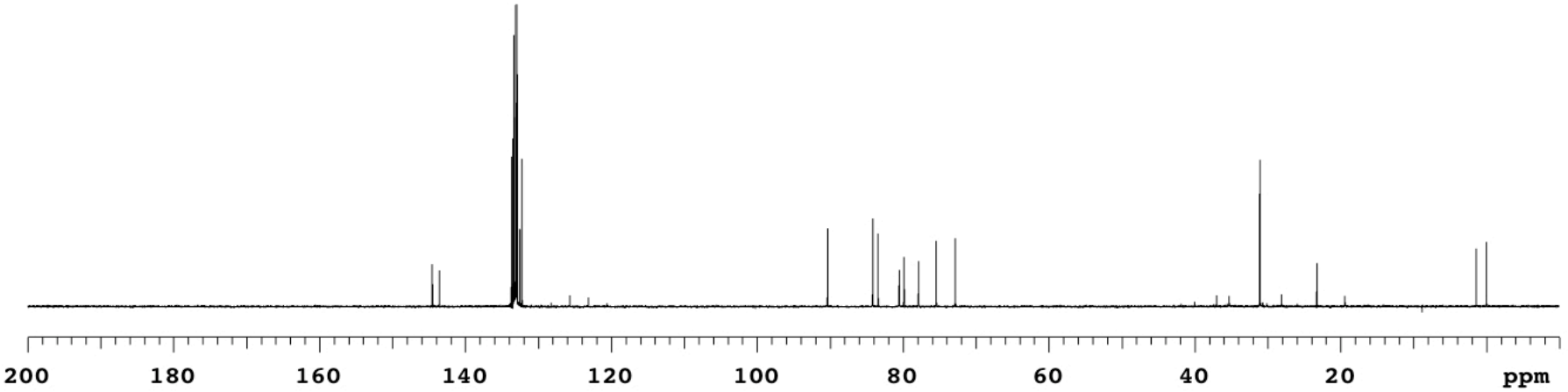
1.125

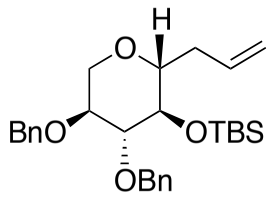
^{1}H NMR, 500 MHz, C_6D_6



1.125

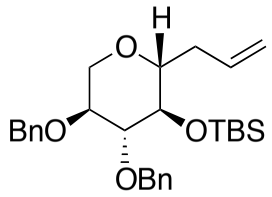
^{13}C NMR, 125 MHz, C_6D_6





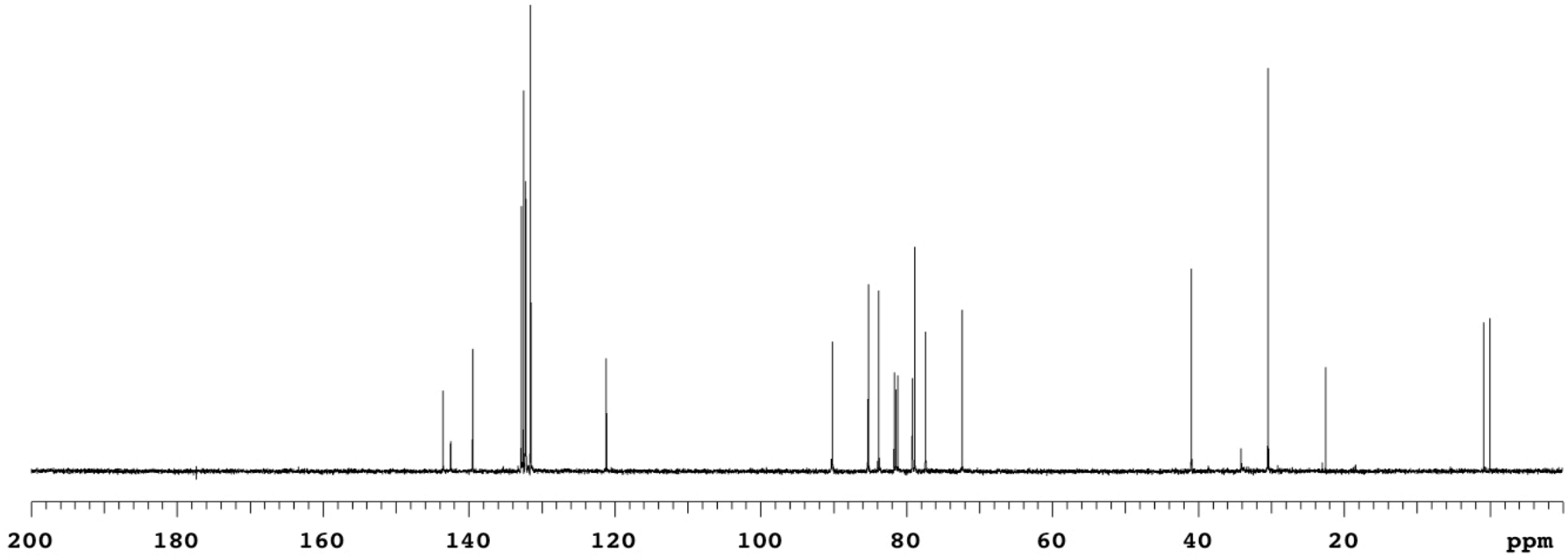
1.127

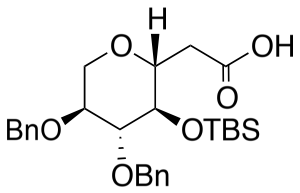
^{1}H NMR, 500 MHz, $CDCl_3$



1.127

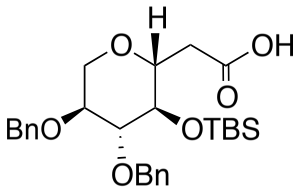
^{13}C NMR, 125 MHz, $CDCl_3$





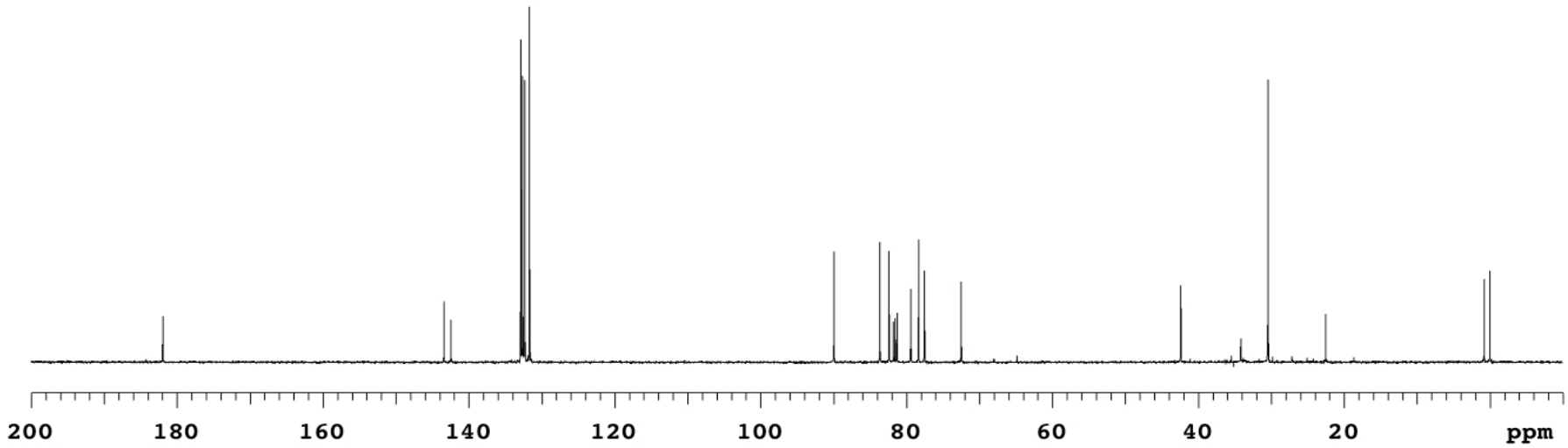
1.120

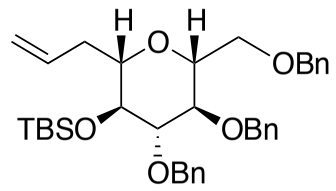
^{1}H NMR, 500 MHz, $CDCl_3$



1.120

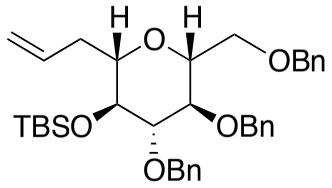
^{13}C NMR, 125 MHz, $CDCl_3$





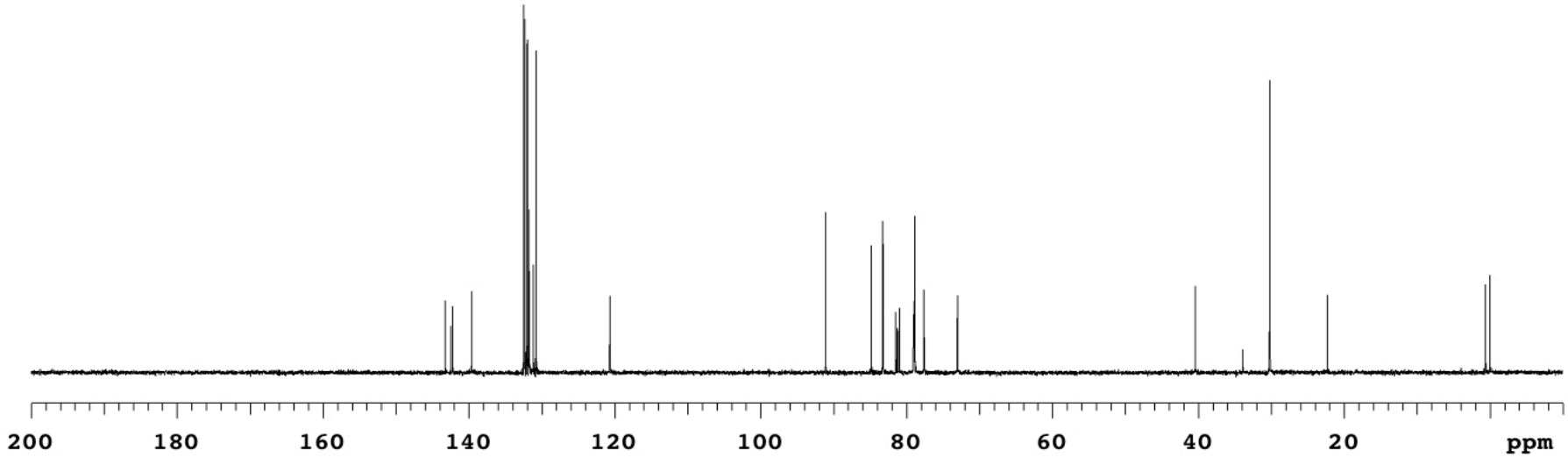
1.130

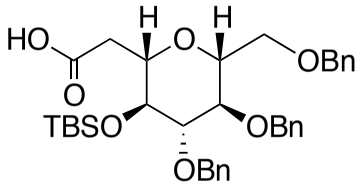
^{1}H NMR, 500 MHz, $CDCl_3$



1.130

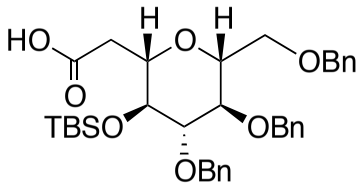
^{13}C NMR, 125 MHz, $CDCl_3$





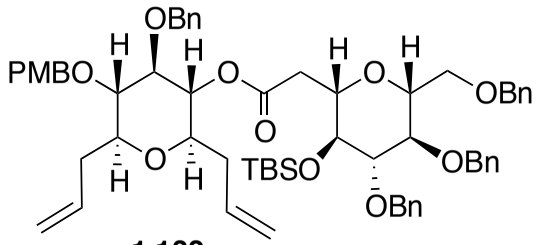
1.121

^{1}H NMR, 500 MHz, $CDCl_3$



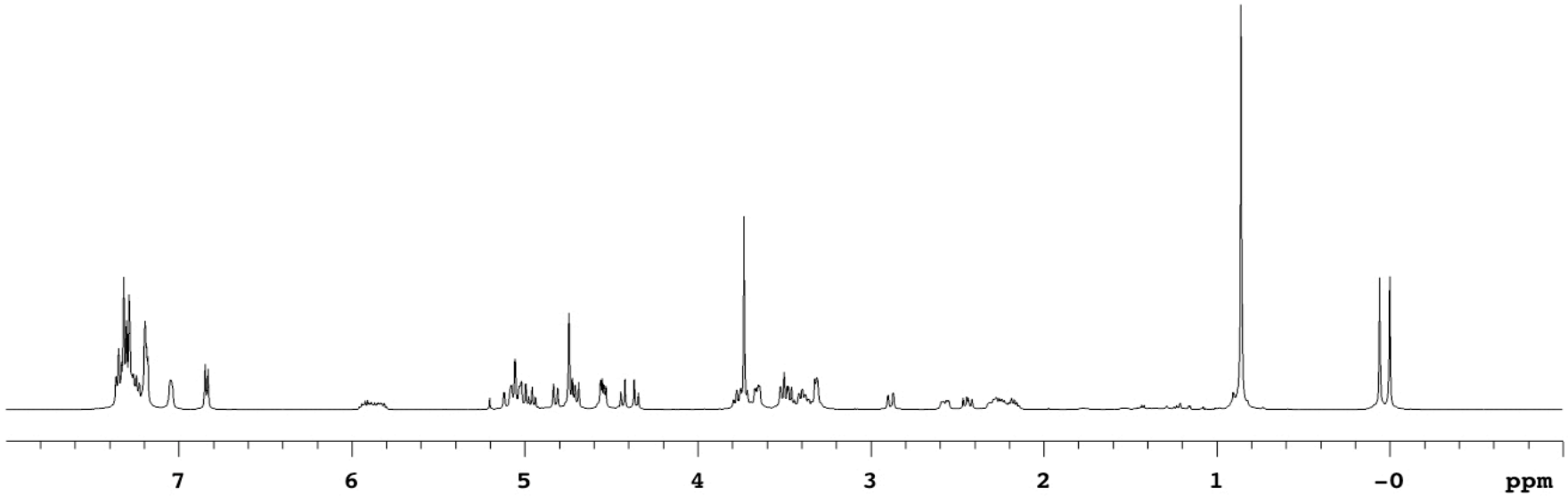
1.121

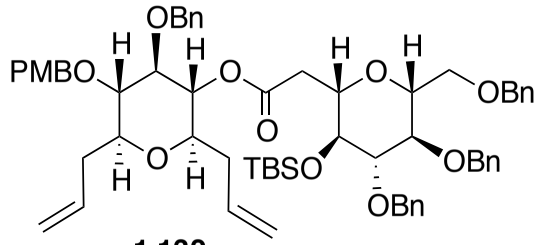
^{13}C NMR, 125 MHz, $CDCl_3$



1.132

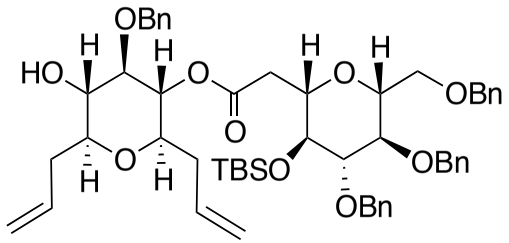
^{1}H NMR, 500 MHz, CD_2Cl_2





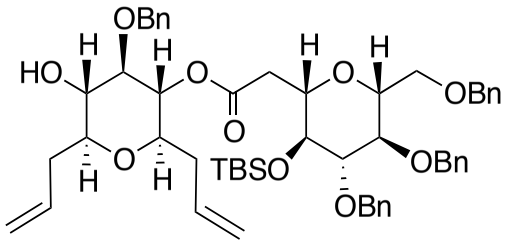
1.132

^{13}C NMR, 125 MHz, CD_2Cl_2



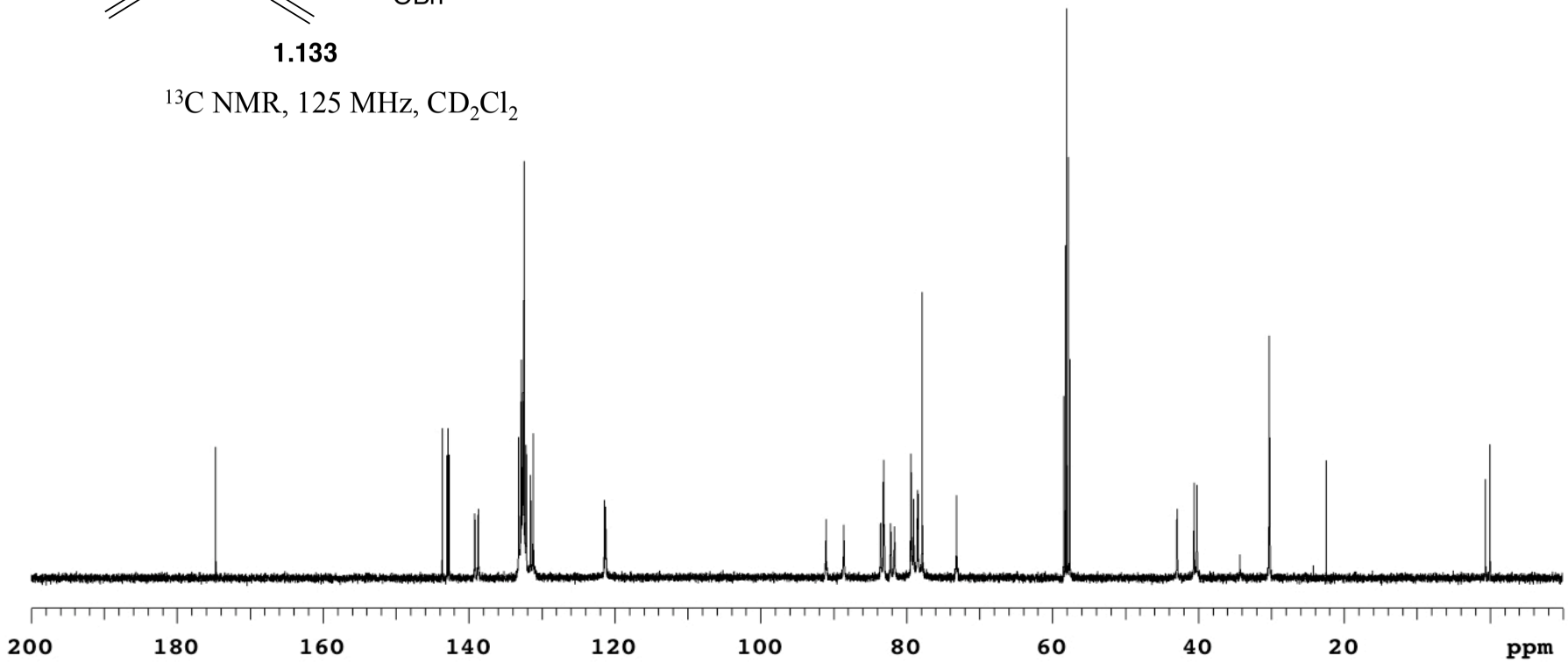
1.133

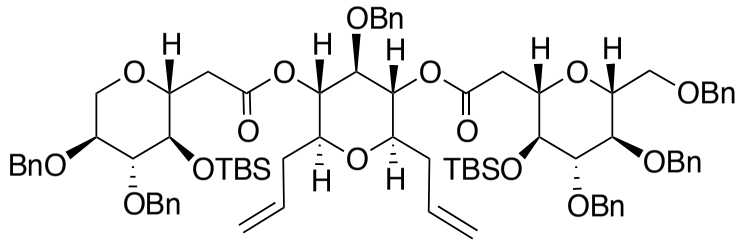
^{1}H NMR, 500 MHz, CD_2Cl_2



1.133

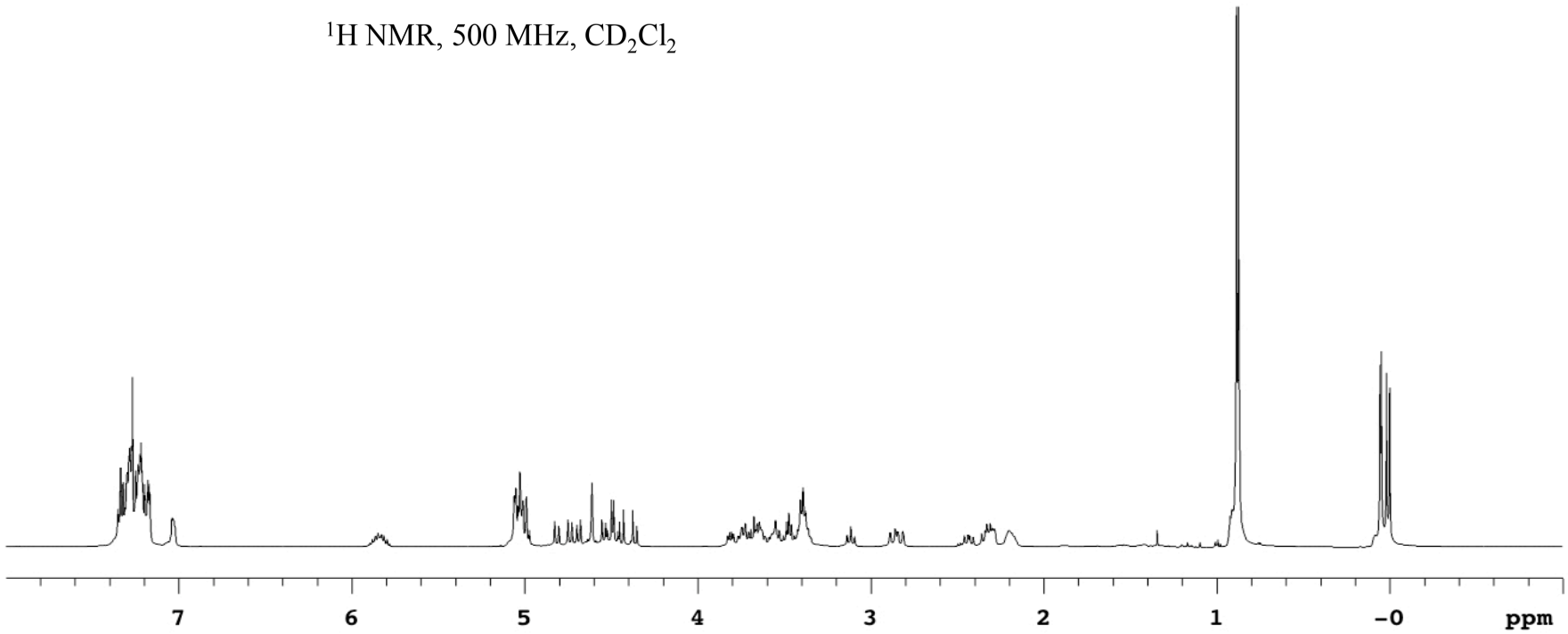
^{13}C NMR, 125 MHz, CD_2Cl_2

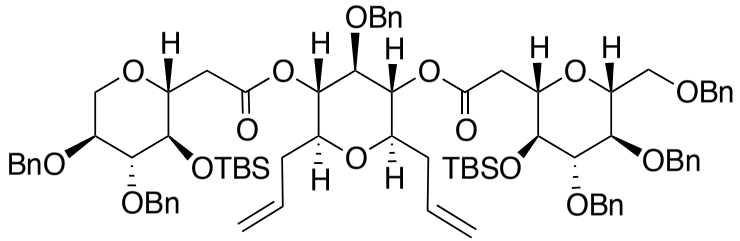




1.119

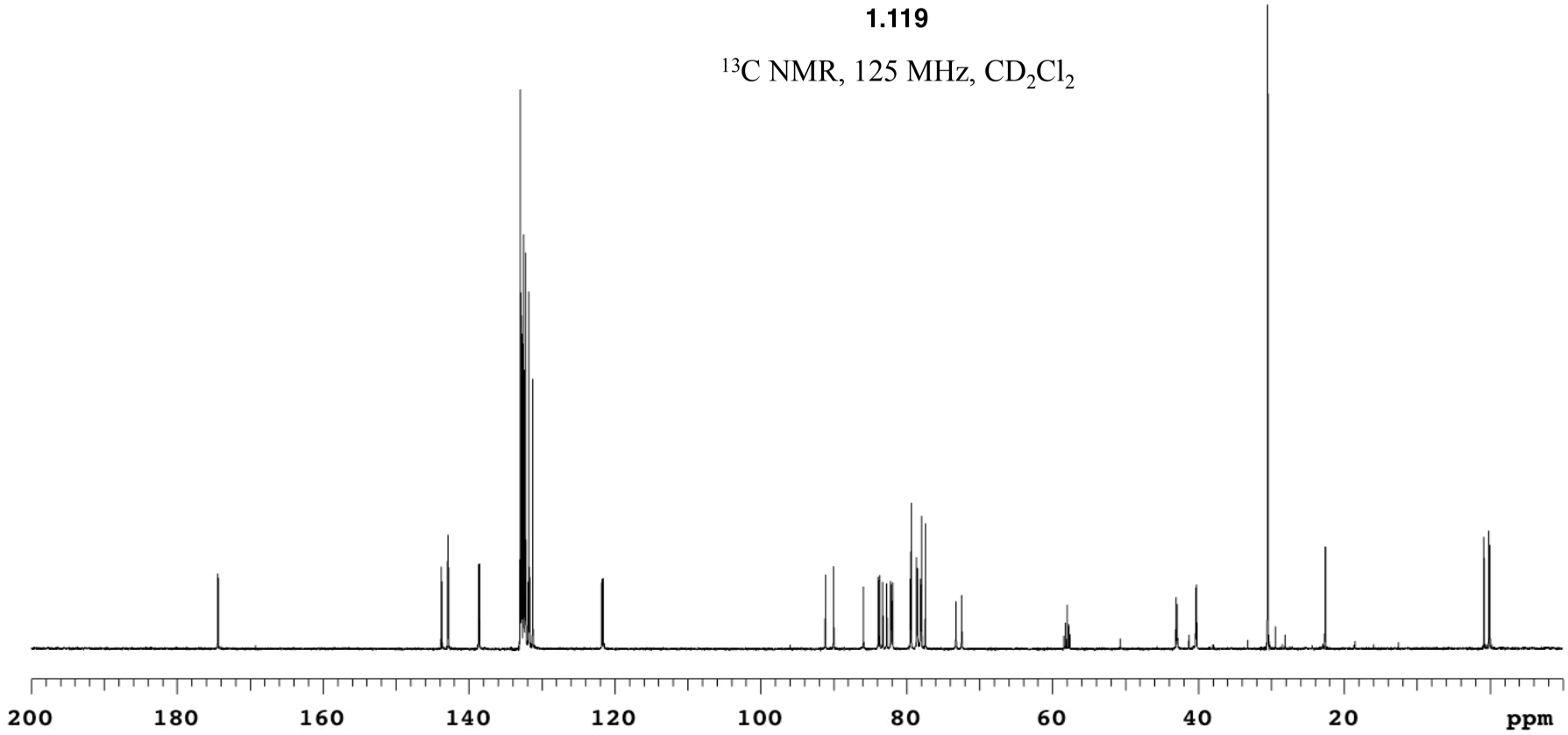
^{1}H NMR, 500 MHz, CD_2Cl_2

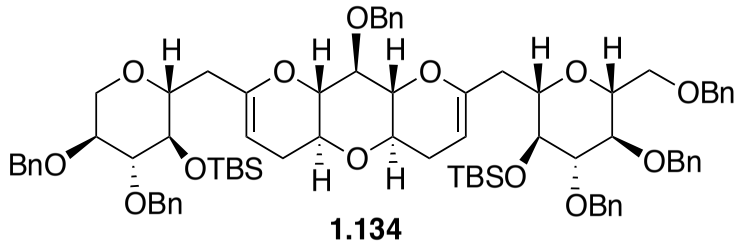




1.119

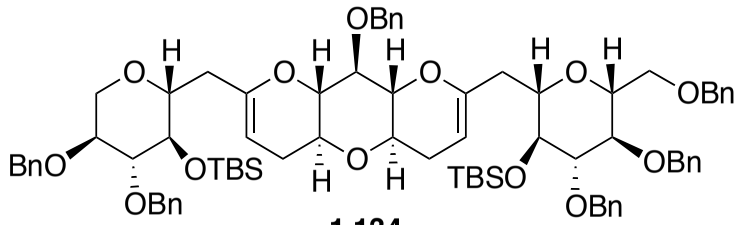
^{13}C NMR, 125 MHz, CD_2Cl_2





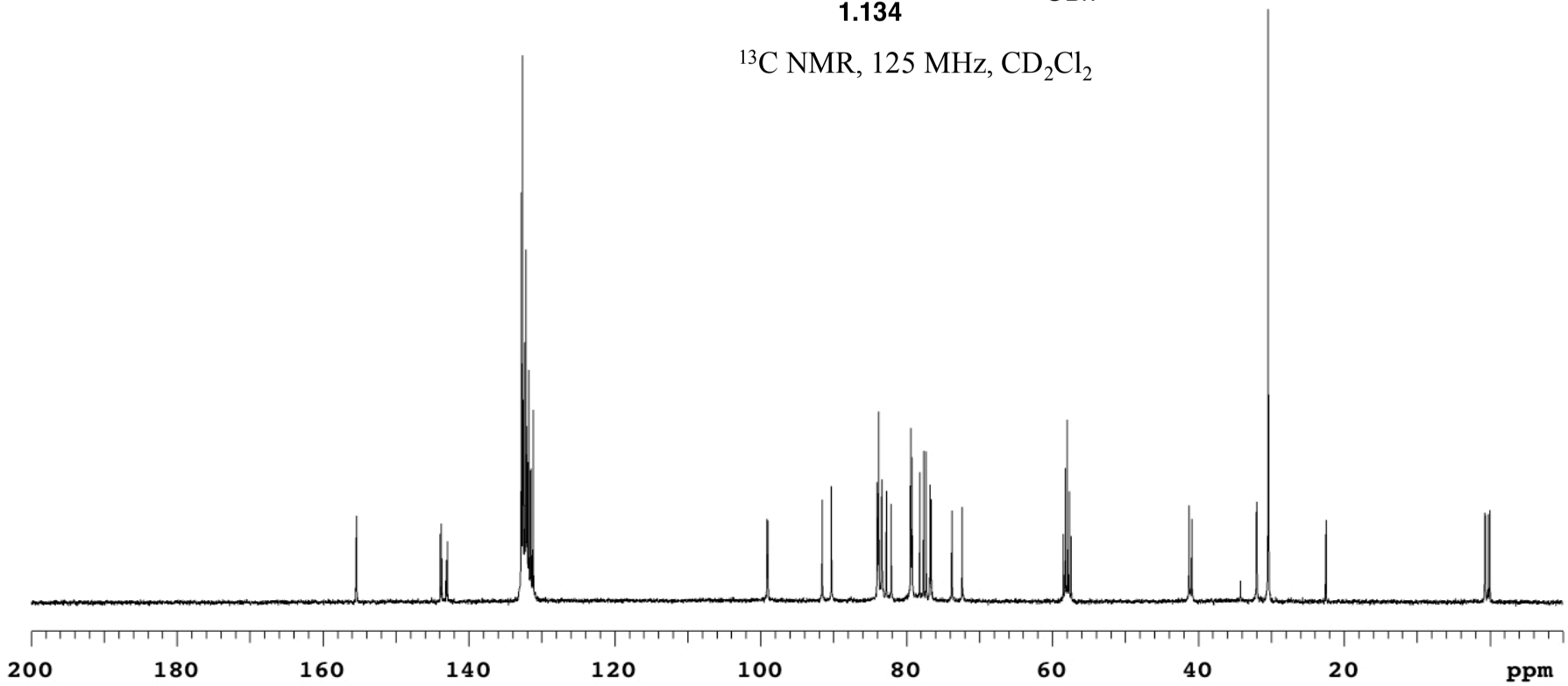
1.134

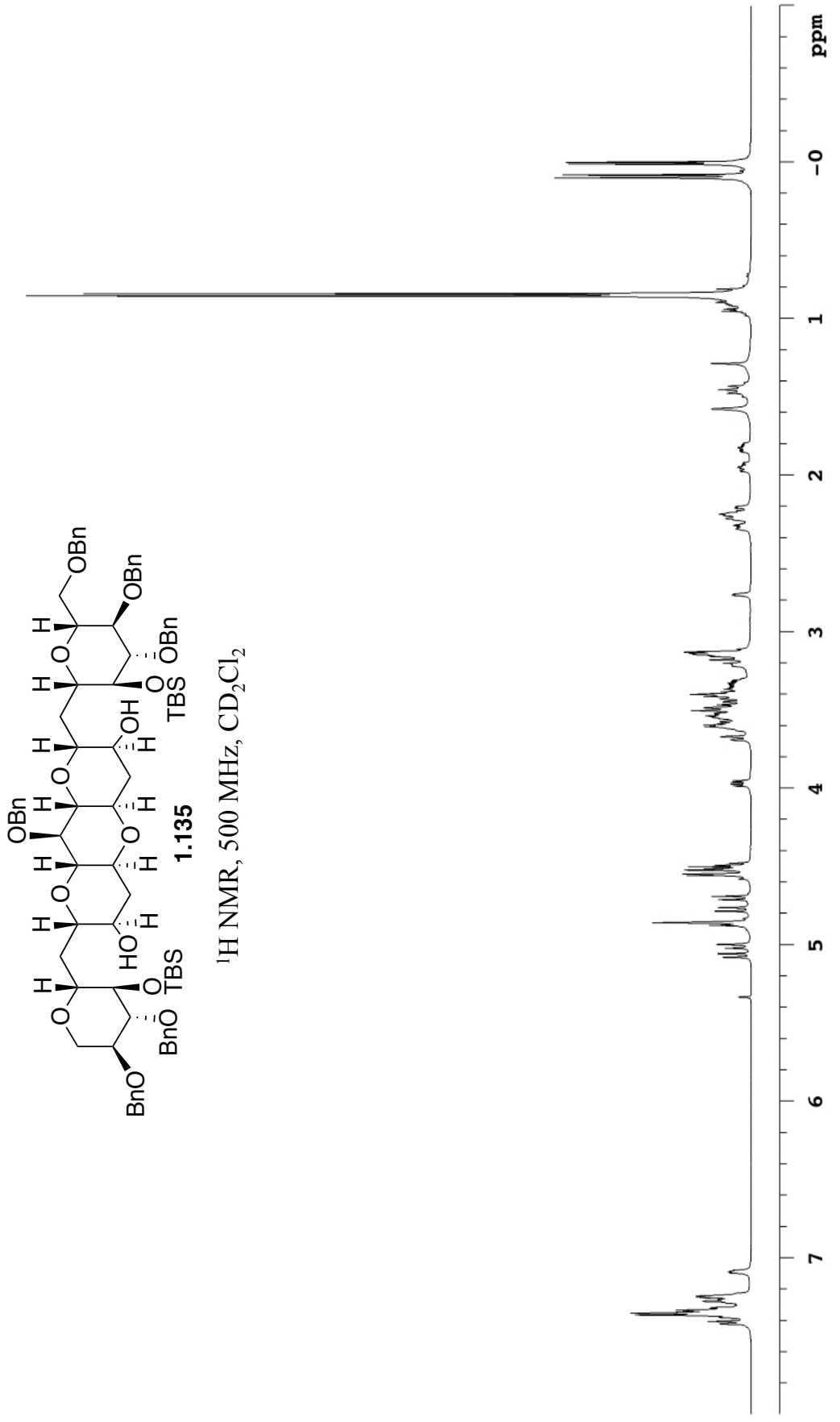
^{1}H NMR, 500 MHz, CD_2Cl_2



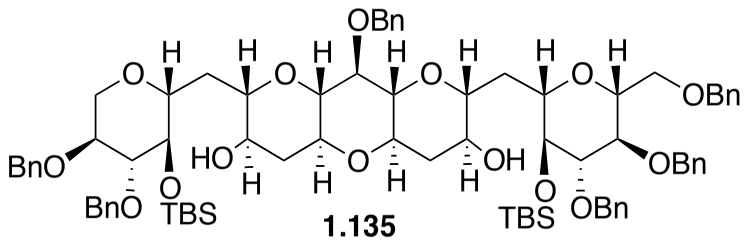
1.134

^{13}C NMR, 125 MHz, CD_2Cl_2



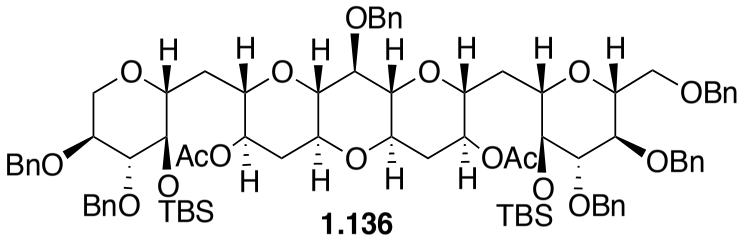


^{1}H NMR, 500 MHz, CD_2Cl_2



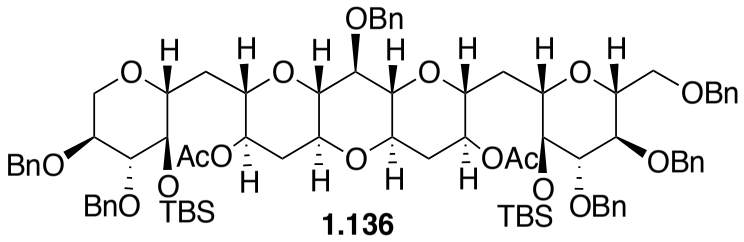
1.135

^{13}C NMR, 125 MHz, CD_2Cl_2

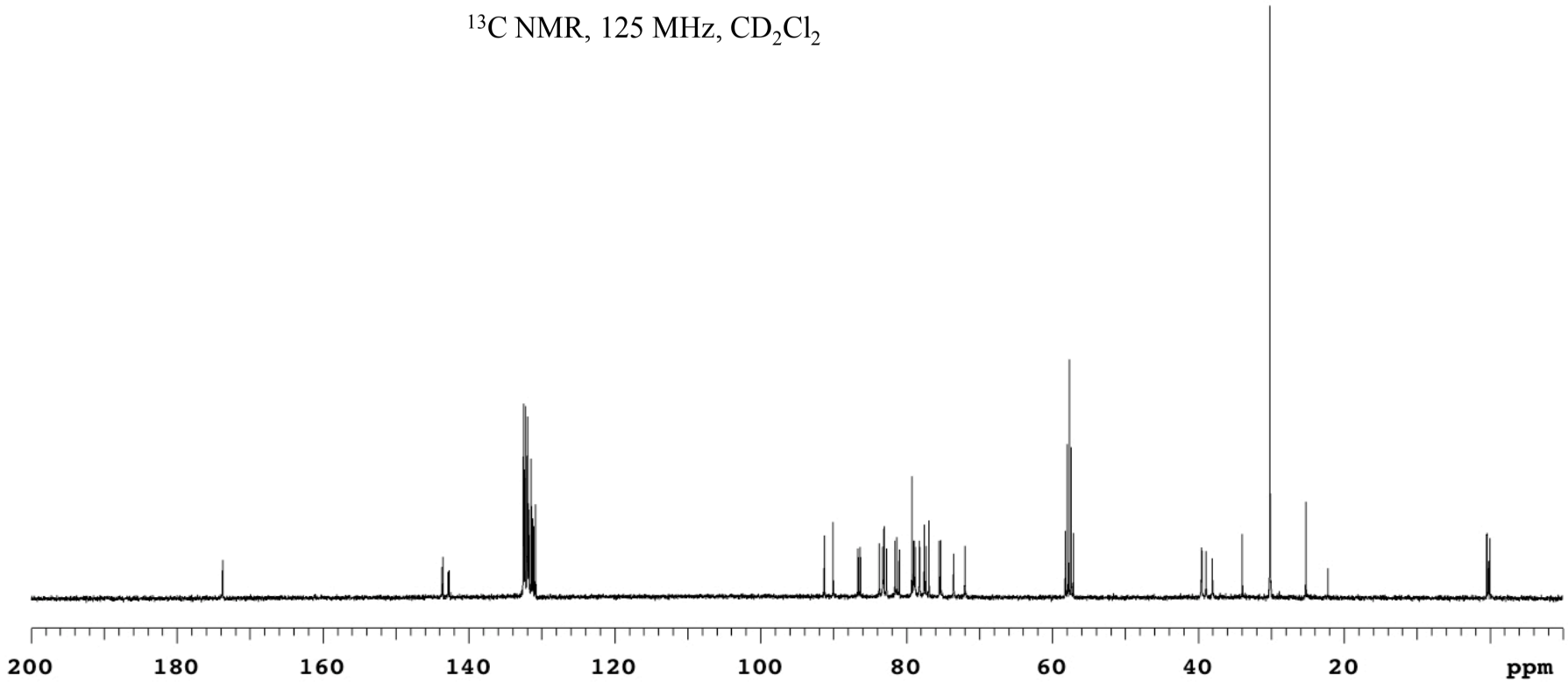


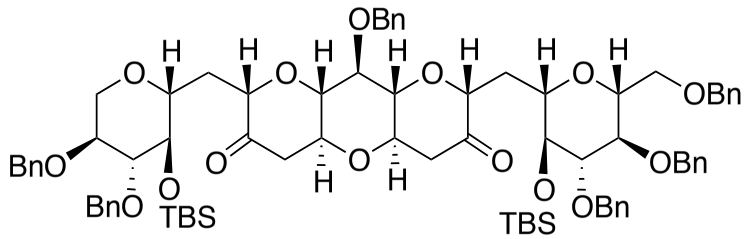
1.136

^{1}H NMR, 500 MHz, C_7D_8



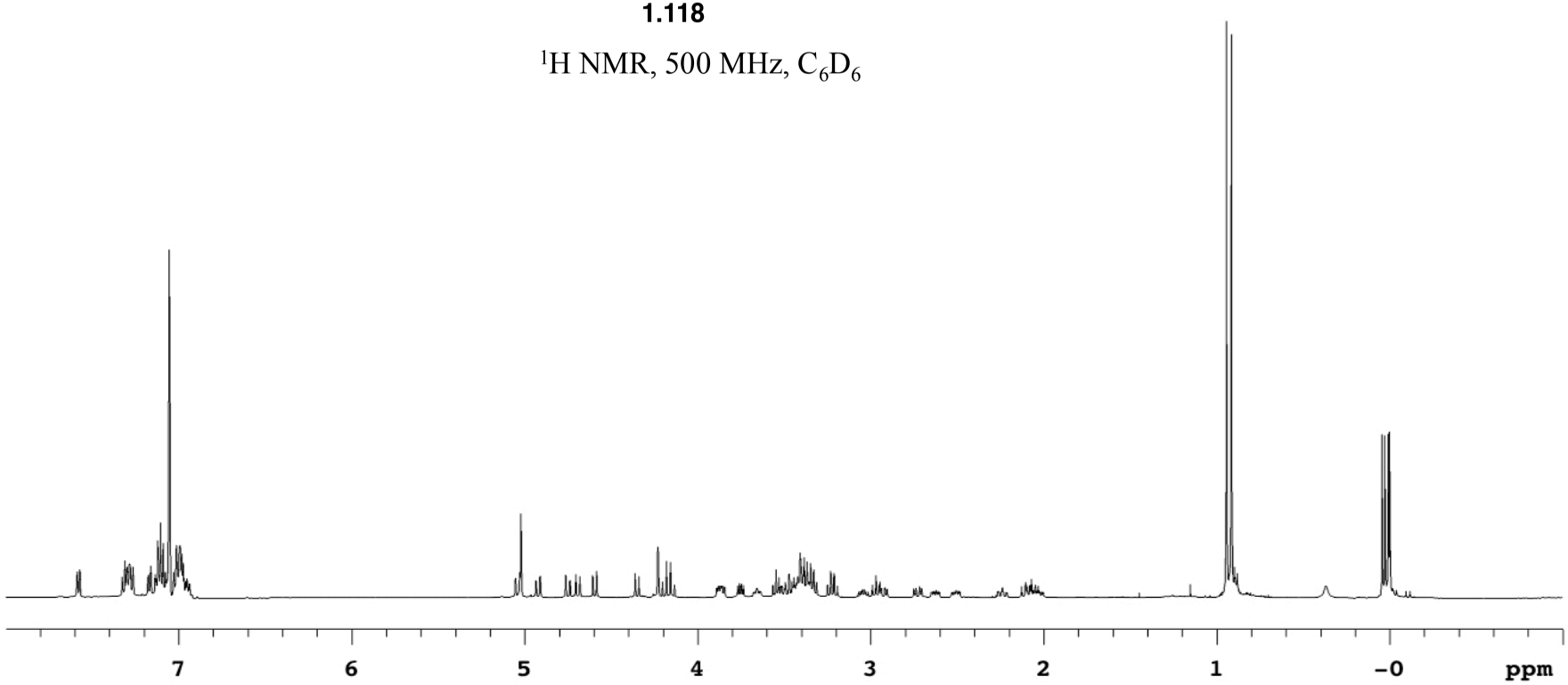
^{13}C NMR, 125 MHz, CD_2Cl_2

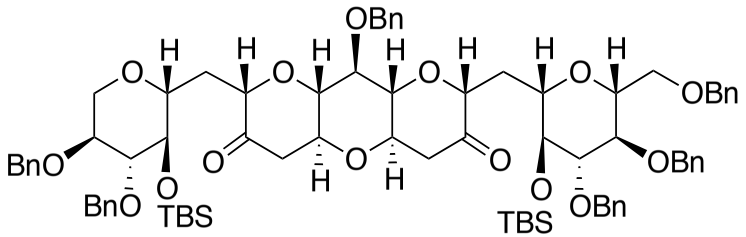




1.118

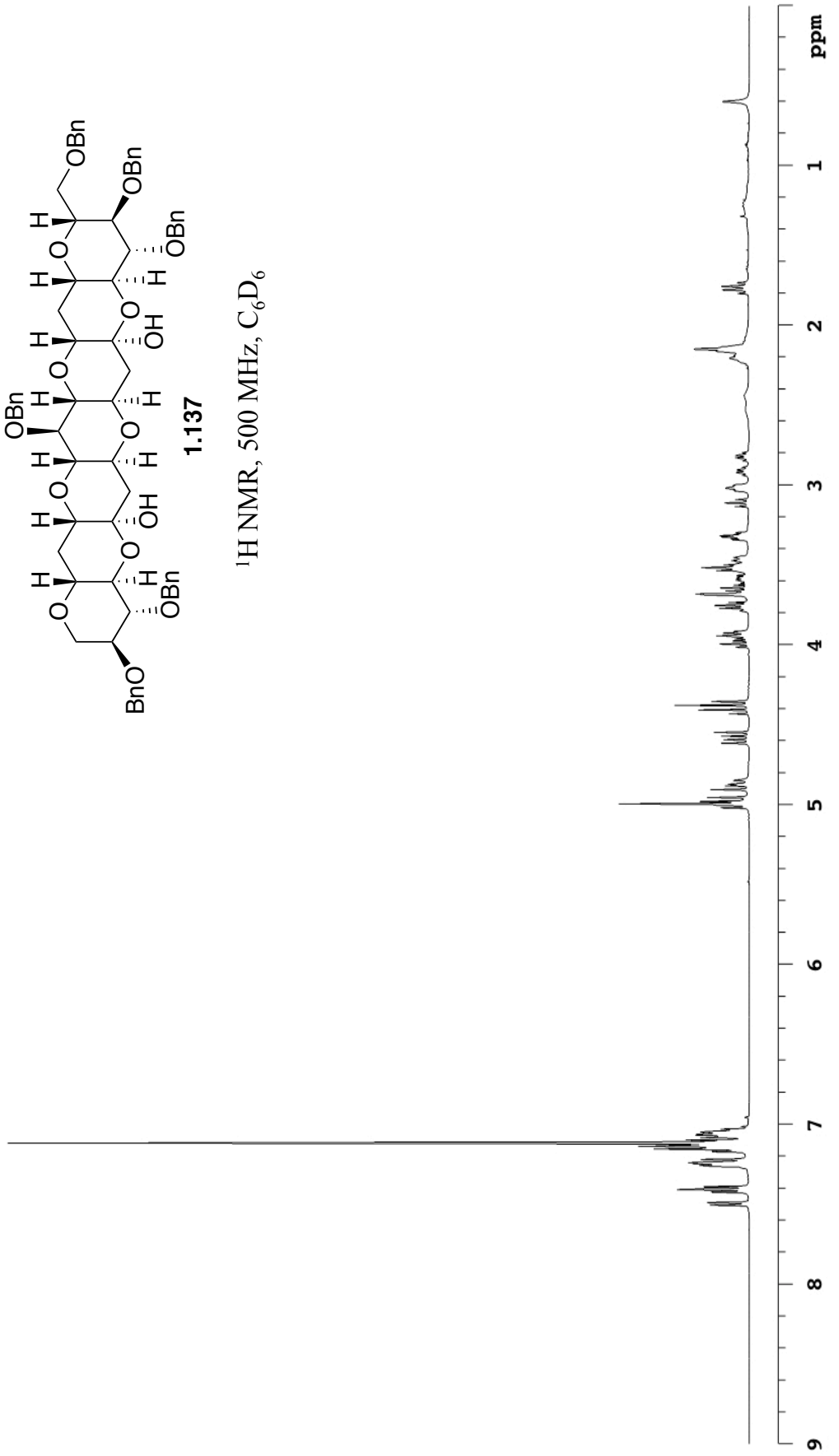
^{1}H NMR, 500 MHz, C_6D_6





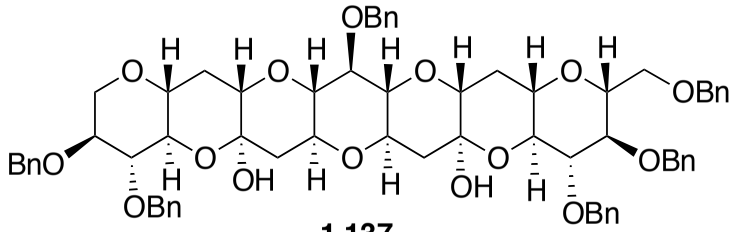
1.118

^{13}C NMR, 125 MHz, CD_2Cl_2



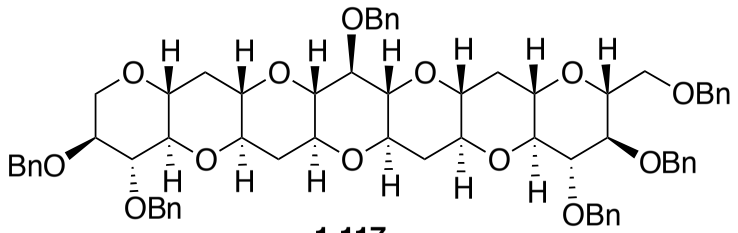
1.137

^{1}H NMR, 500 MHz, C_6D_6



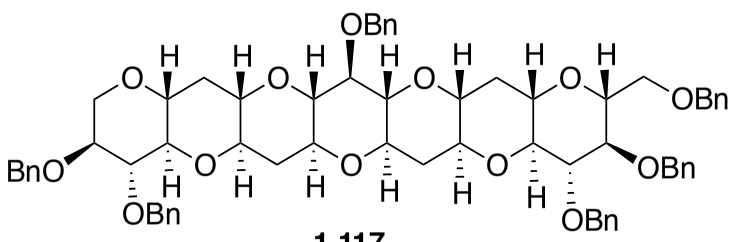
1.137

^{13}C NMR, 125 MHz, CD_2Cl_2



1.117

^{1}H NMR, 500 MHz, C_6D_6

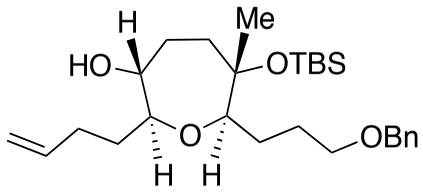


1.117

^{13}C NMR, 125 MHz, CD_2Cl_2

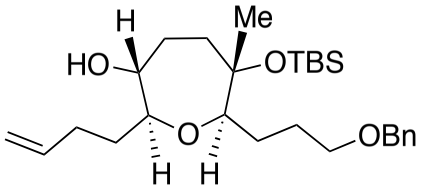
APPENDIX B

^{1}H AND ^{13}C NMR SPECTRA CHAPTER 2



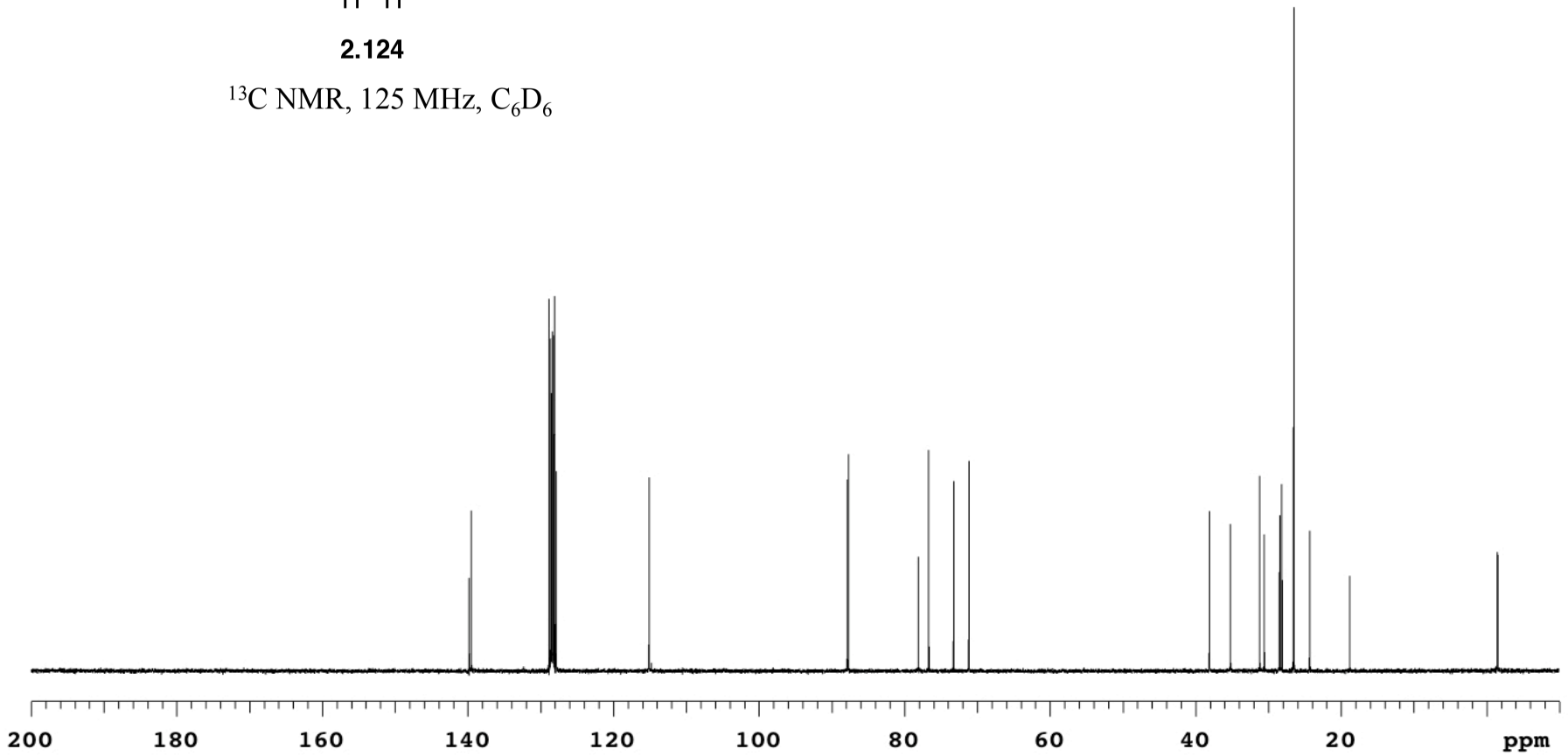
2.124

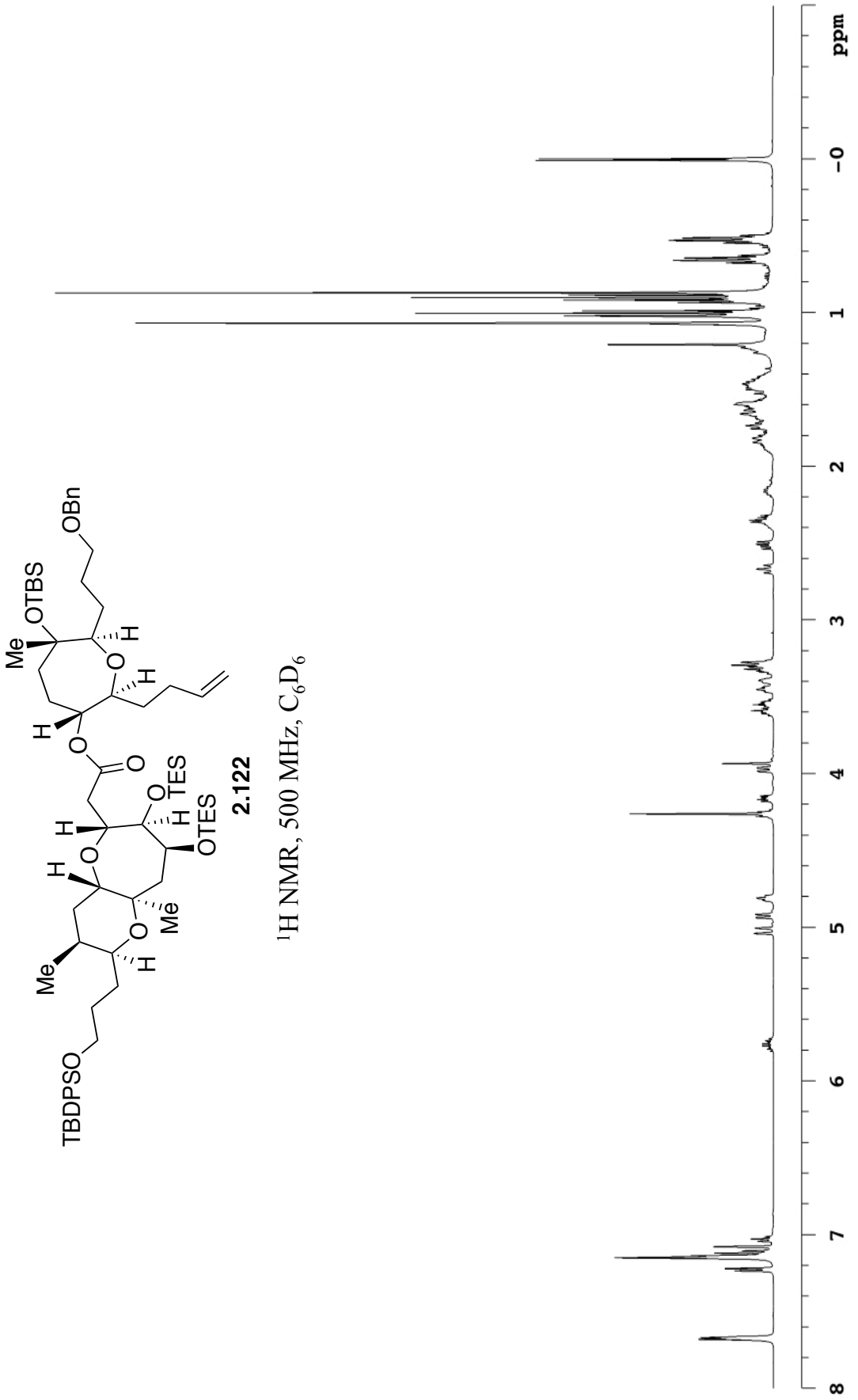
^{1}H NMR, 500 MHz, C_6D_6



2.124

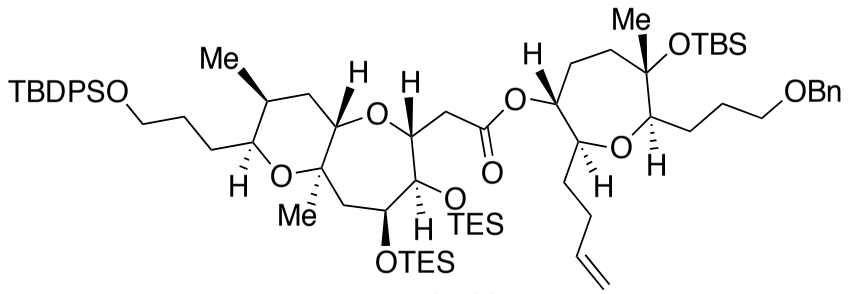
^{13}C NMR, 125 MHz, C_6D_6





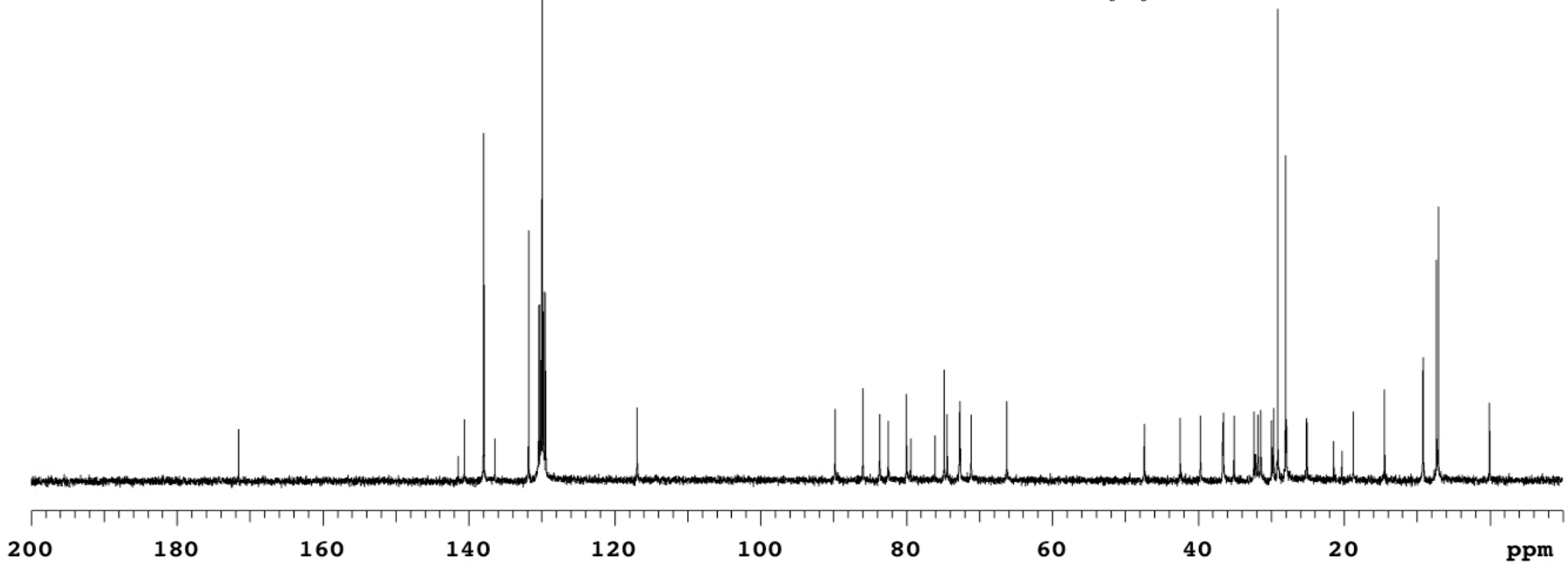
2.122

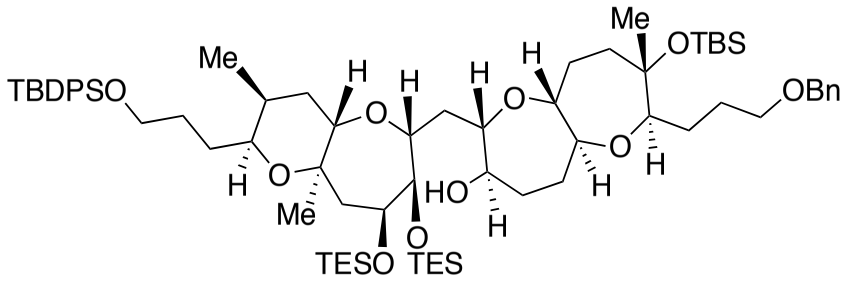
^{1}H NMR, 500 MHz, C_6D_6



2.122

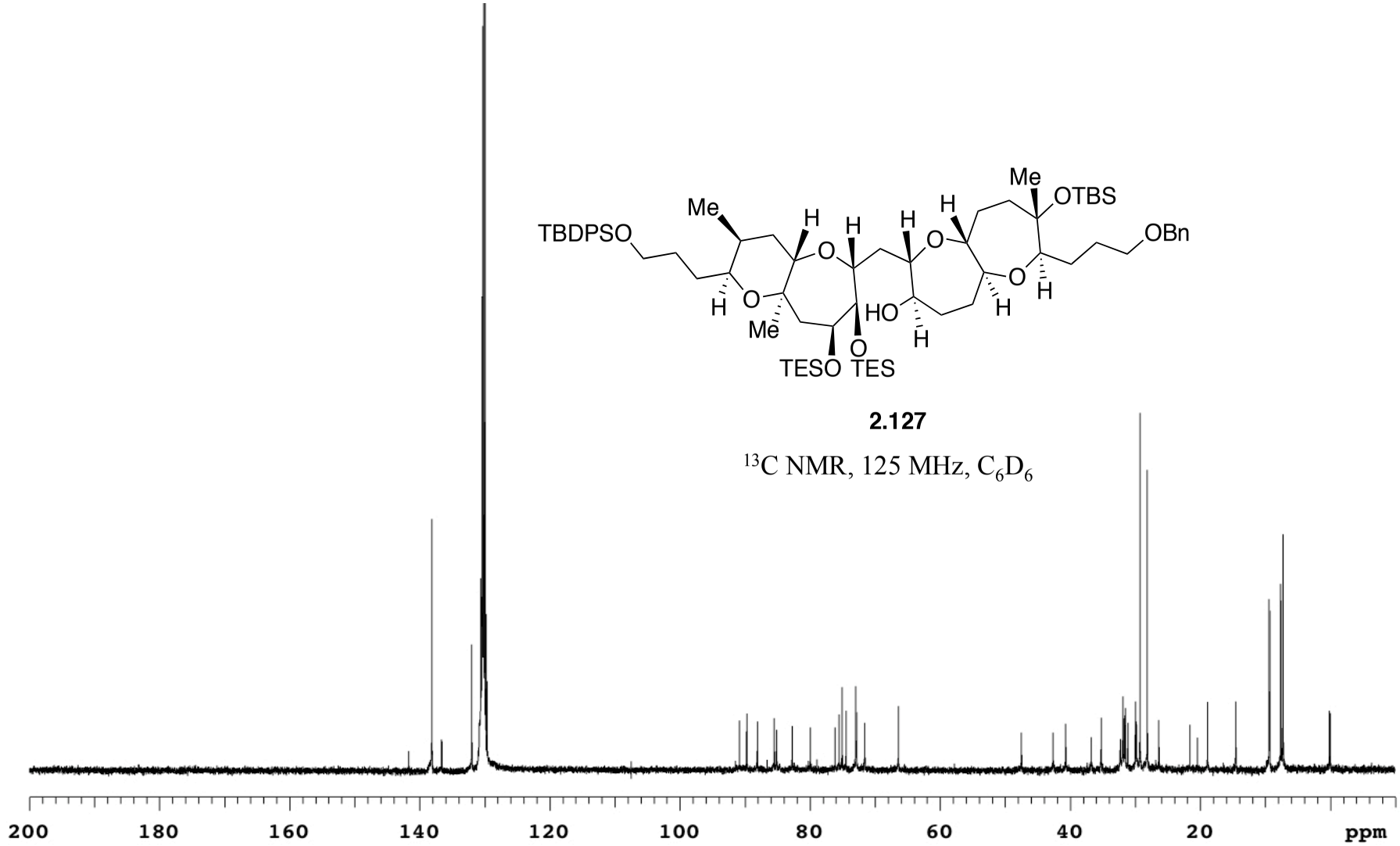
^{13}C NMR, 125 MHz, C_6D_6





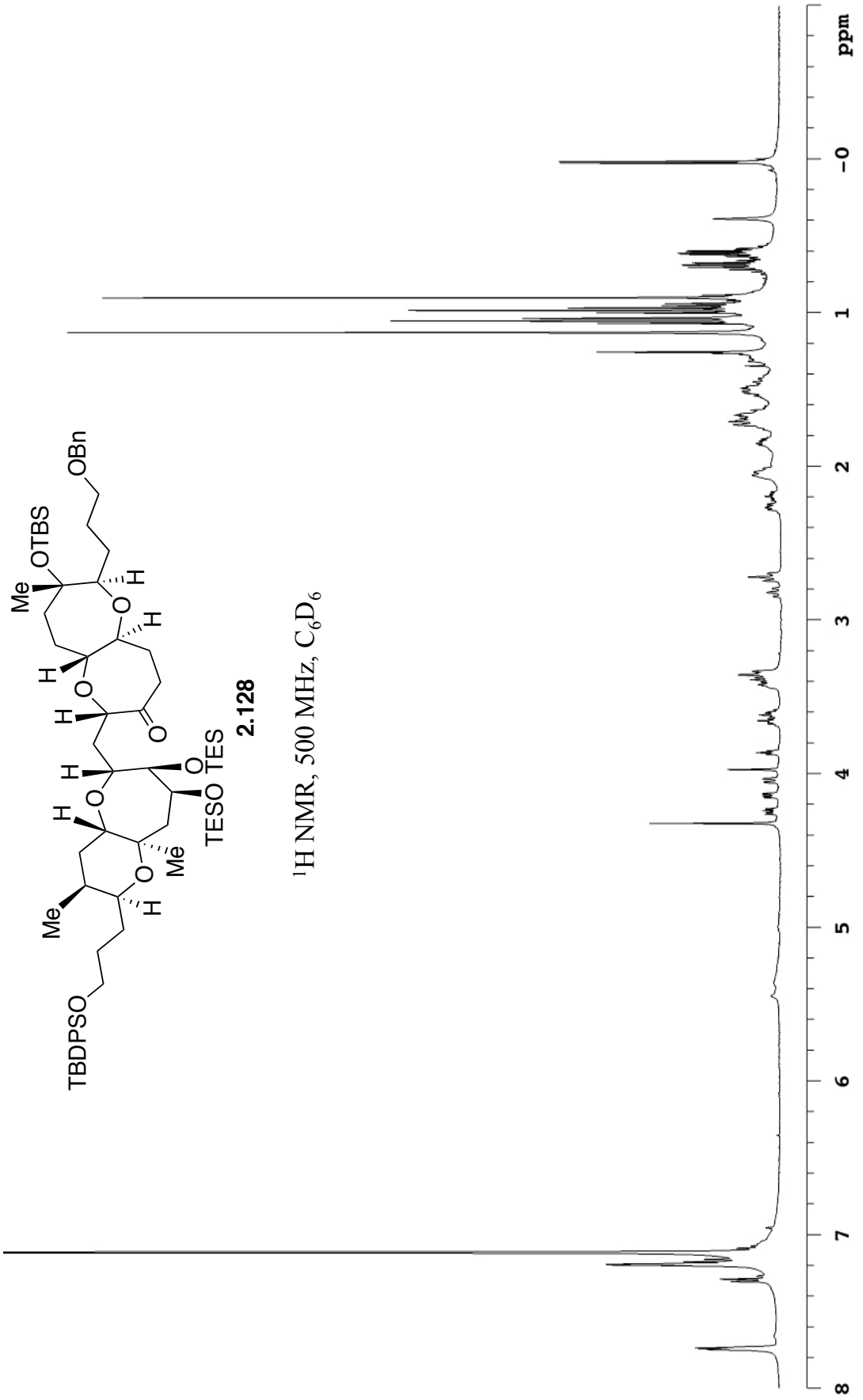
2.127

^{1}H NMR, 500 MHz, C_6D_6



2.127

^{13}C NMR, 125 MHz, C_6D_6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TESO TES
H
O
Me
Me
O
H
TBDPSO
2.128
^{1}H NMR, 500 MHz, C_6D_6
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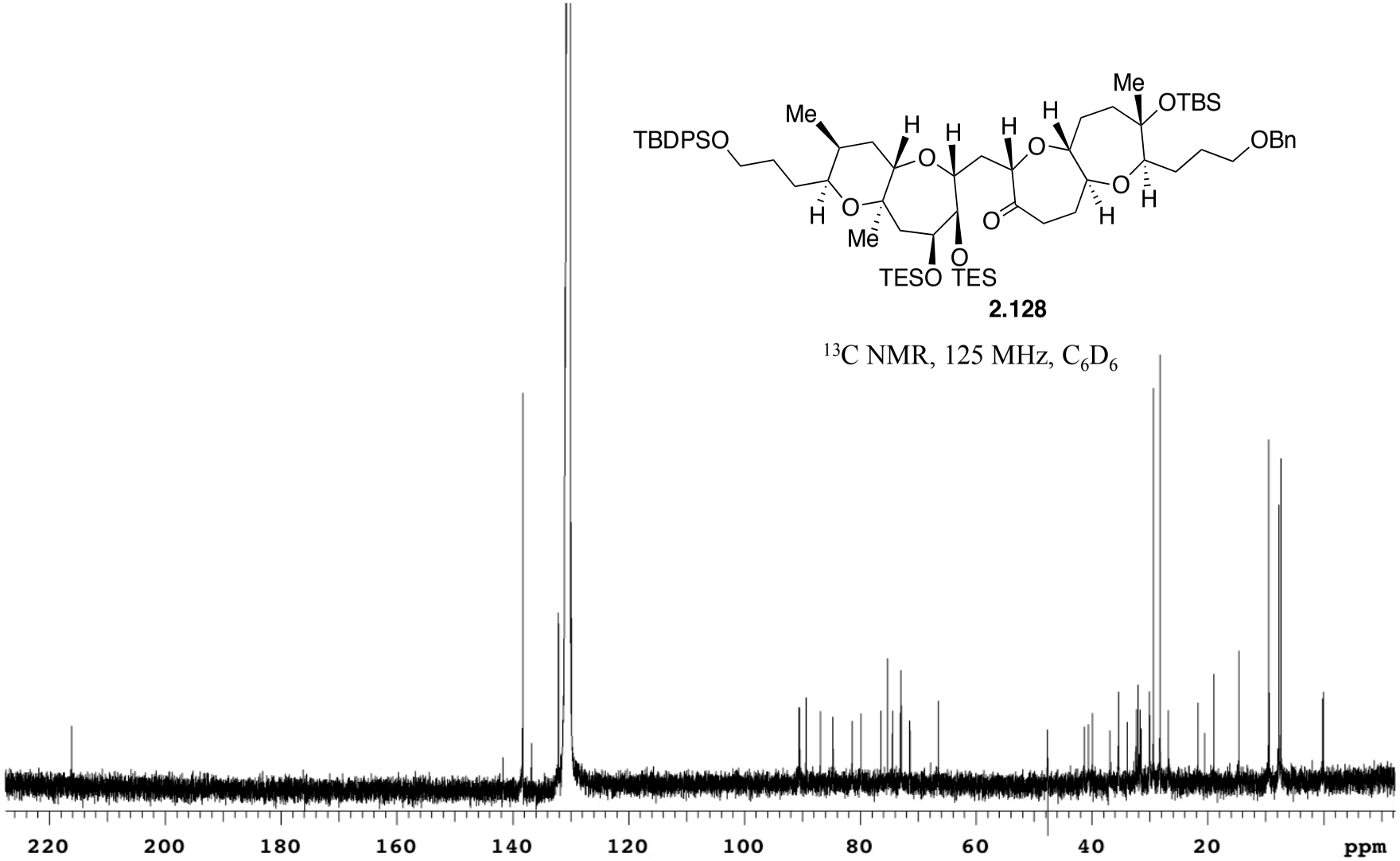
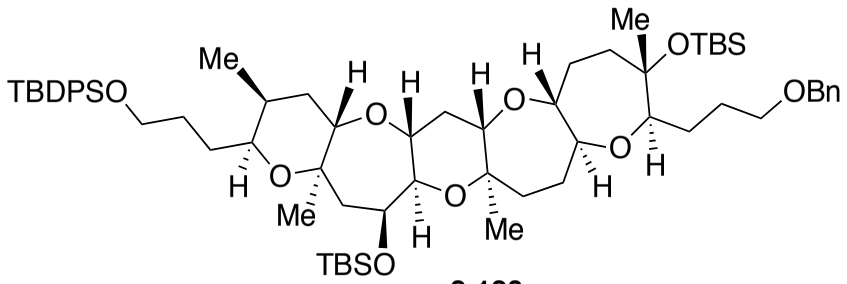
7
6
5
4
3
2
1
−0
ppm



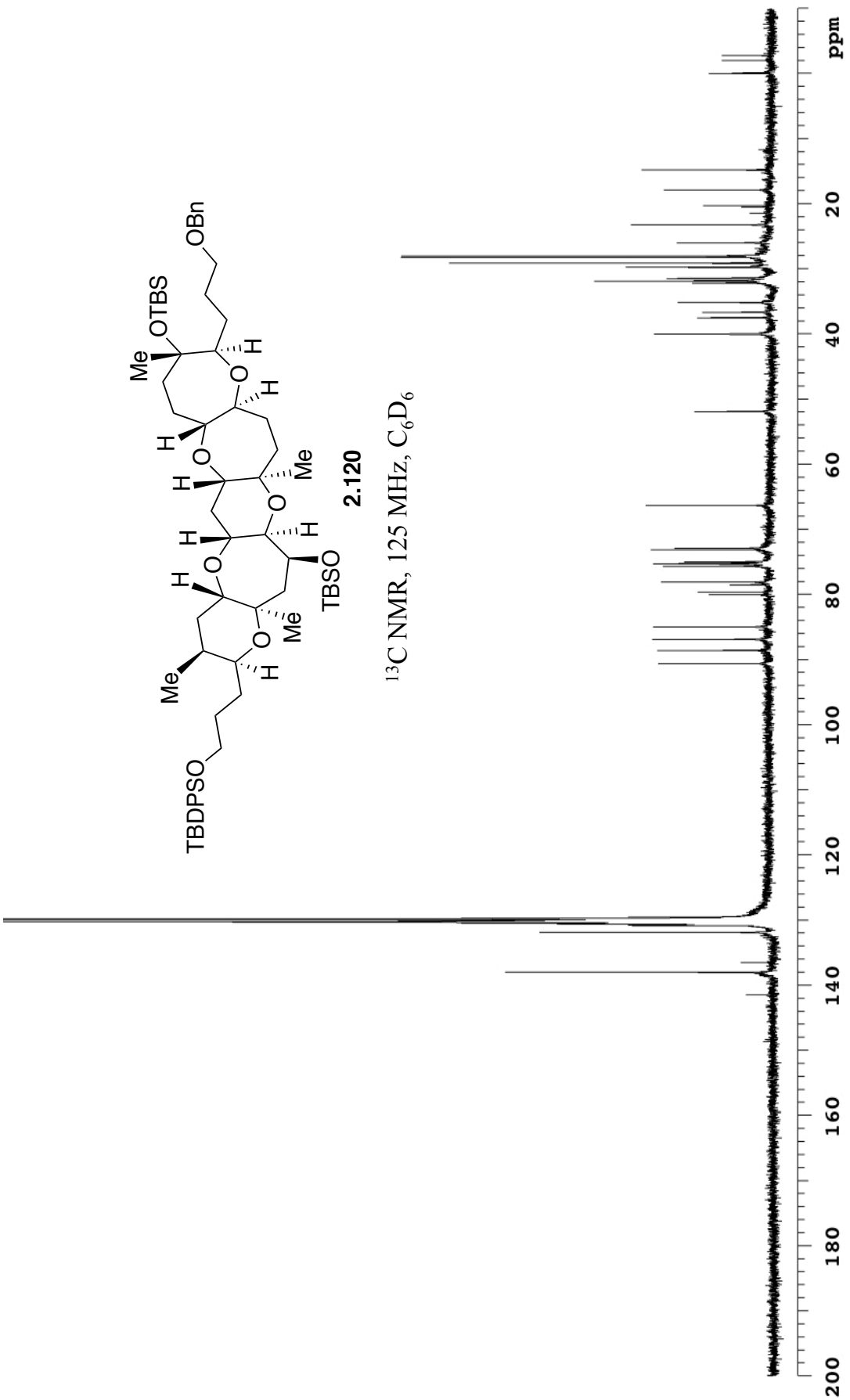
2.128

^{13}C NMR, 125 MHz, C_6D_6



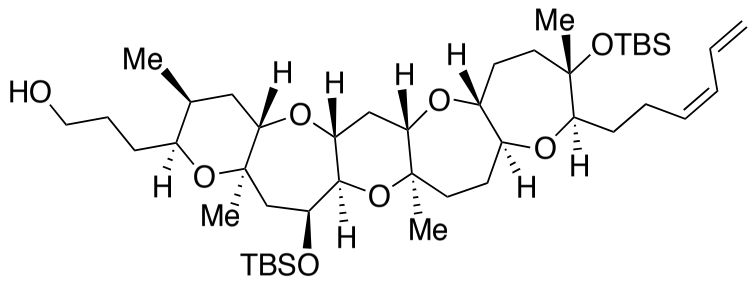
2.120

^{1}H NMR, 500 MHz, C_6D_6



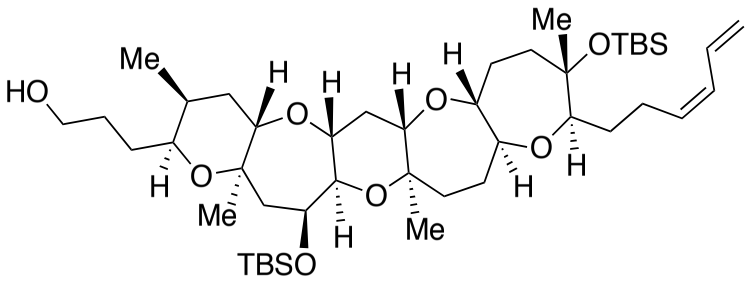
2.120

^{13}C NMR, 125 MHz, C_6D_6



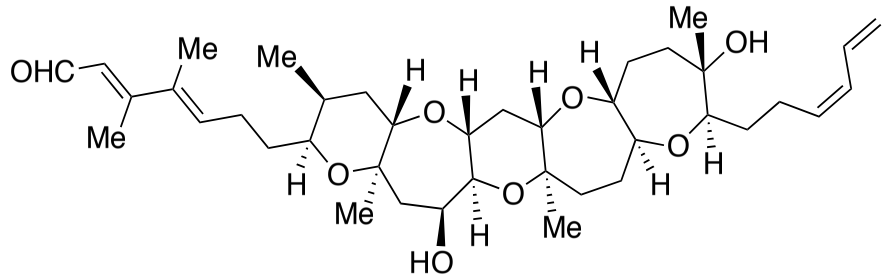
2.133

^{1}H NMR, 500 MHz, $CDCl_3$



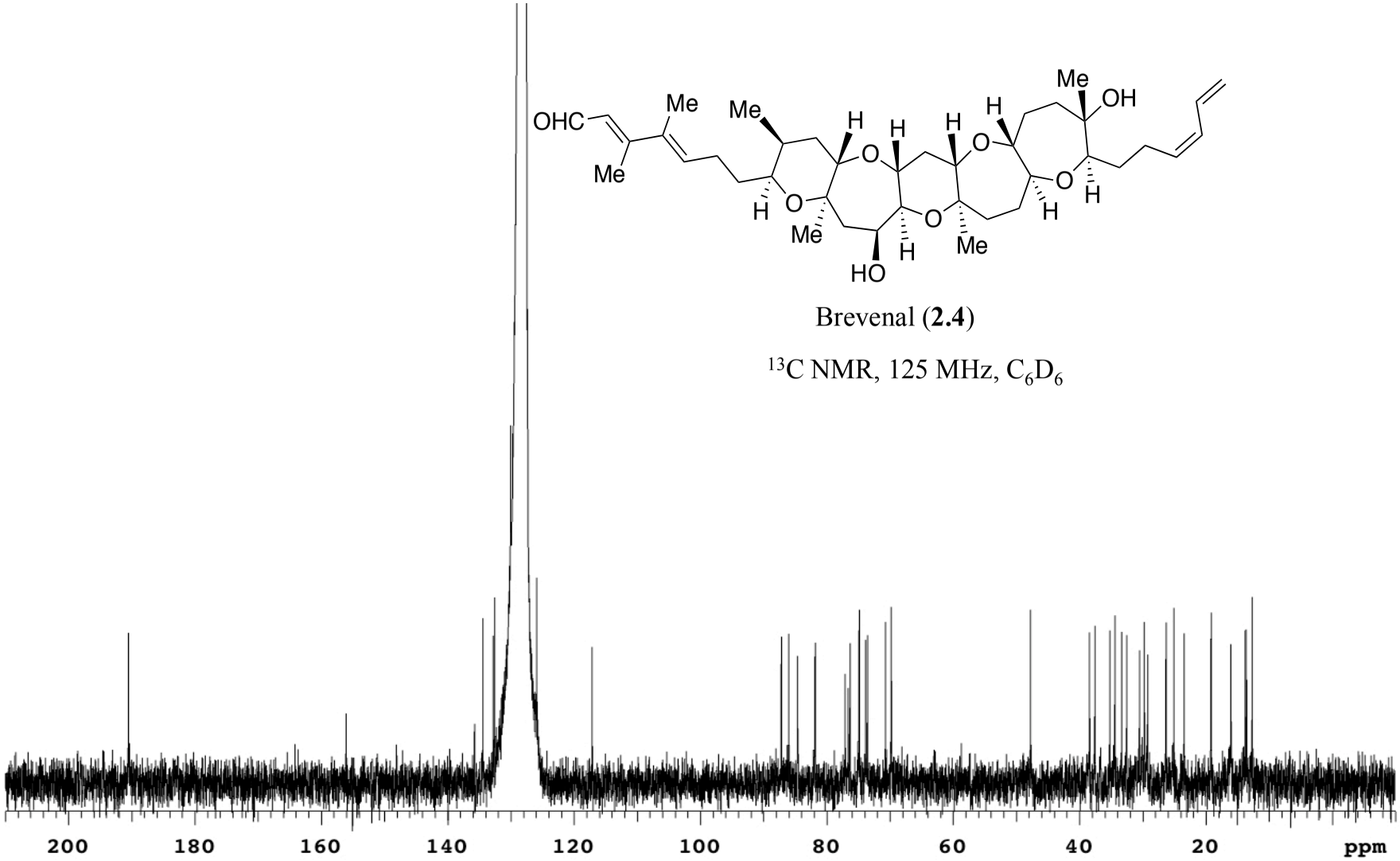
2.133

^{13}C NMR, 100 MHz, $CDCl_3$



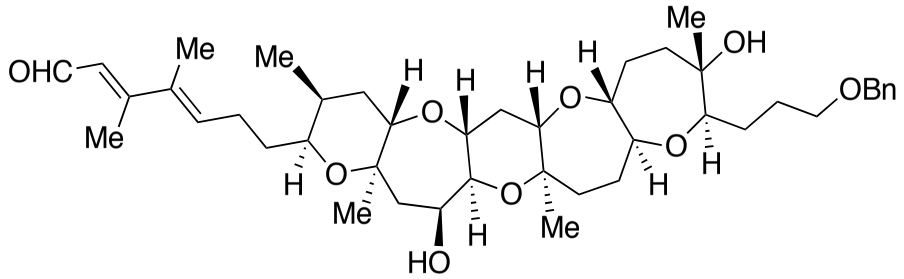
Brevenal (**2.4**)

^{1}H NMR, 500 MHz, C_6D_6



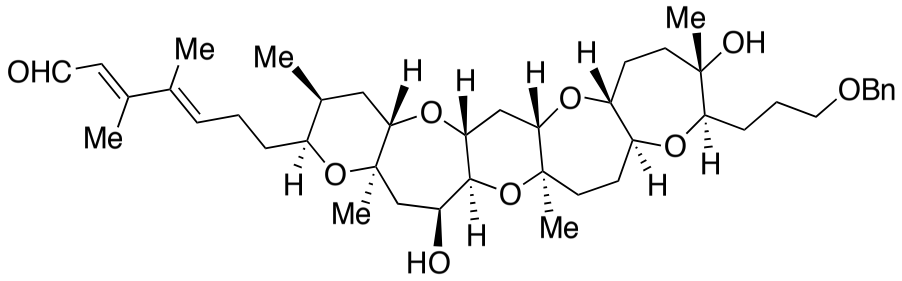
Brevenal (**2.4**)

^{13}C NMR, 125 MHz, C_6D_6



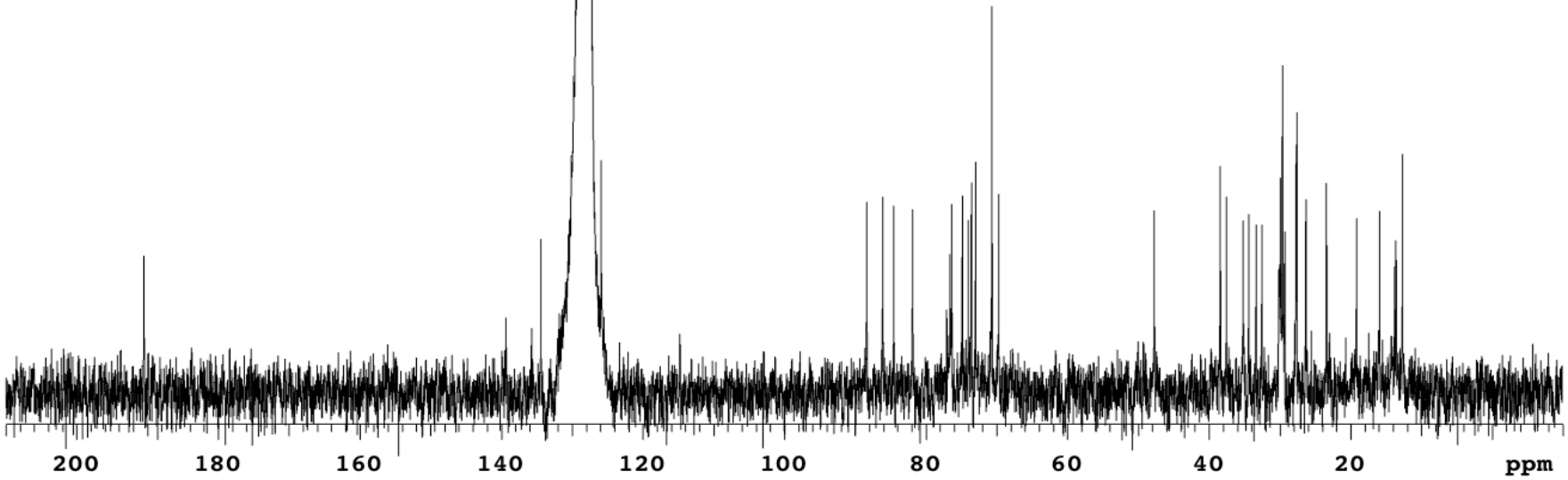
Brevenal analogue (**2.139**)

^{1}H NMR, 500 MHz, C_6D_6



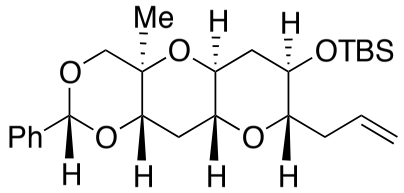
Brevenal analogue (**2.139**)

^{13}C NMR, 100 MHz, C_6D_6



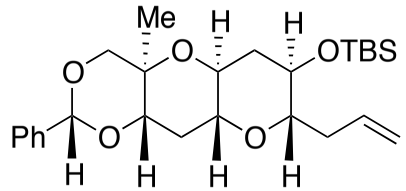
APPENDIX C

^{1}H AND ^{13}C NMR SPECTRA CHAPTER 3



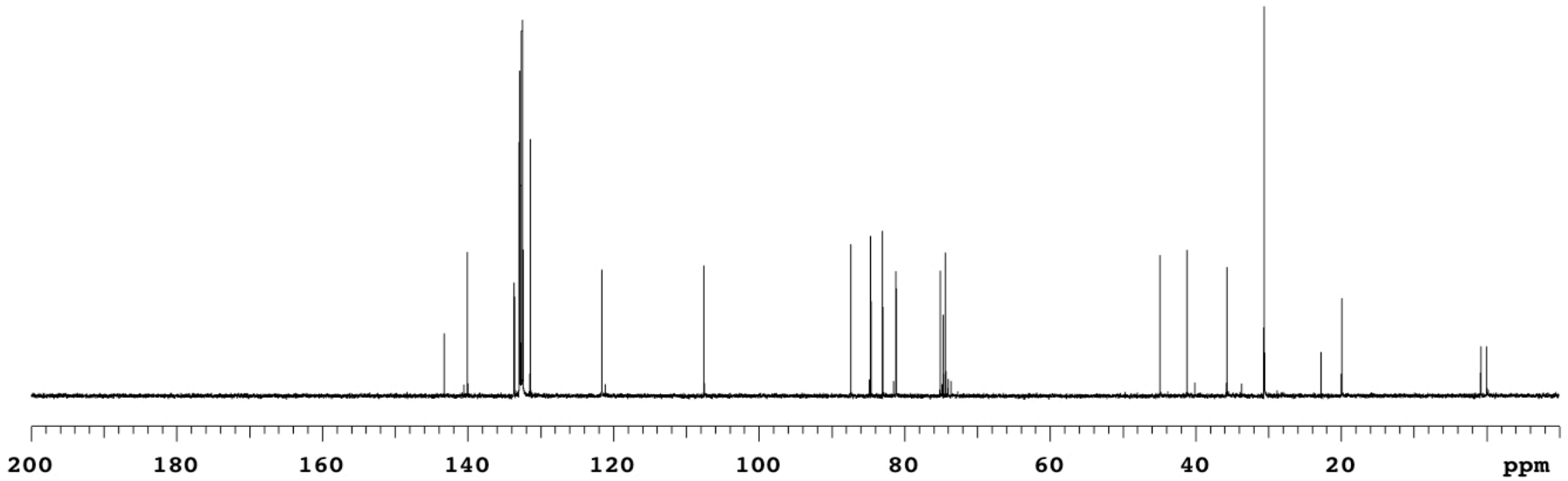
3.89

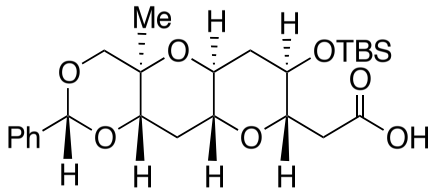
^{1}H NMR, 500 MHz, C_6D_6



3.89

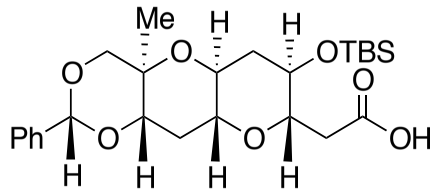
^{13}C NMR, 125 MHz, C_6D_6





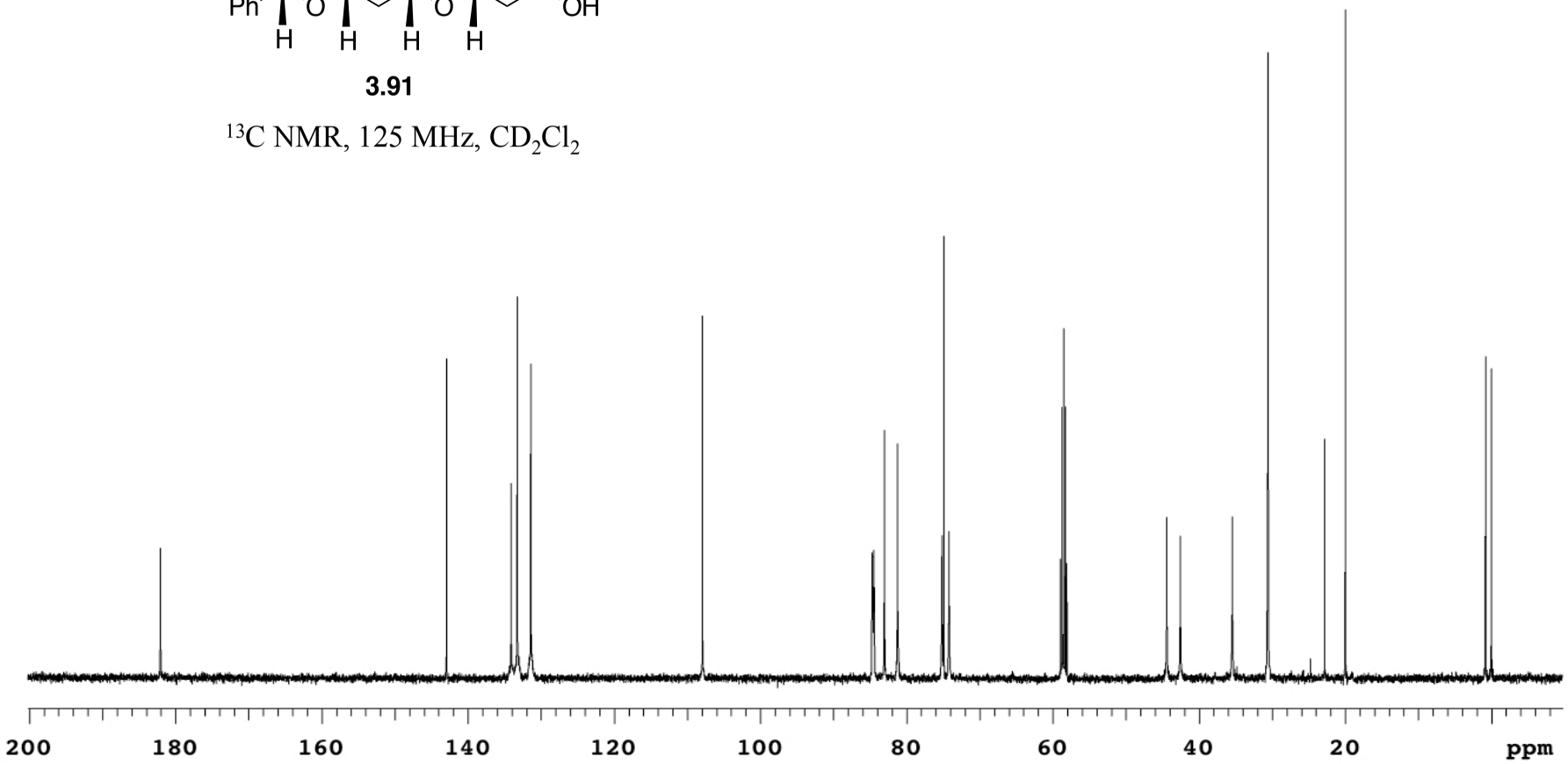
3.91

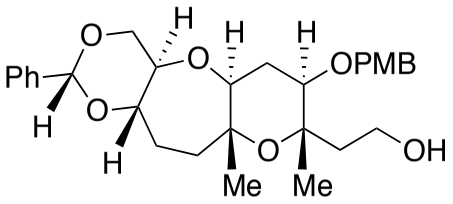
^{1}H NMR, 500 MHz, CD_2Cl_2



3.91

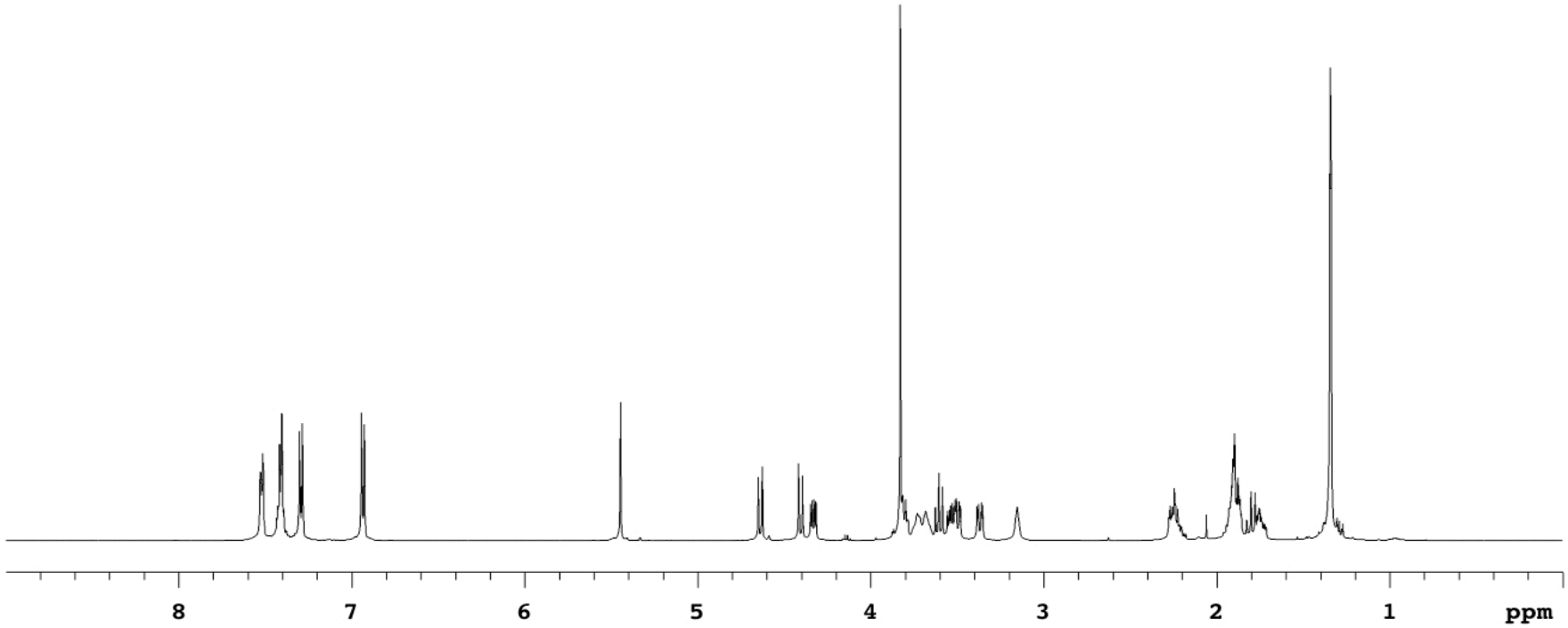
^{13}C NMR, 125 MHz, CD_2Cl_2

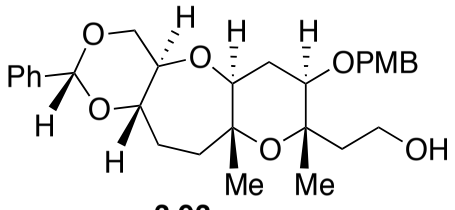




3.93

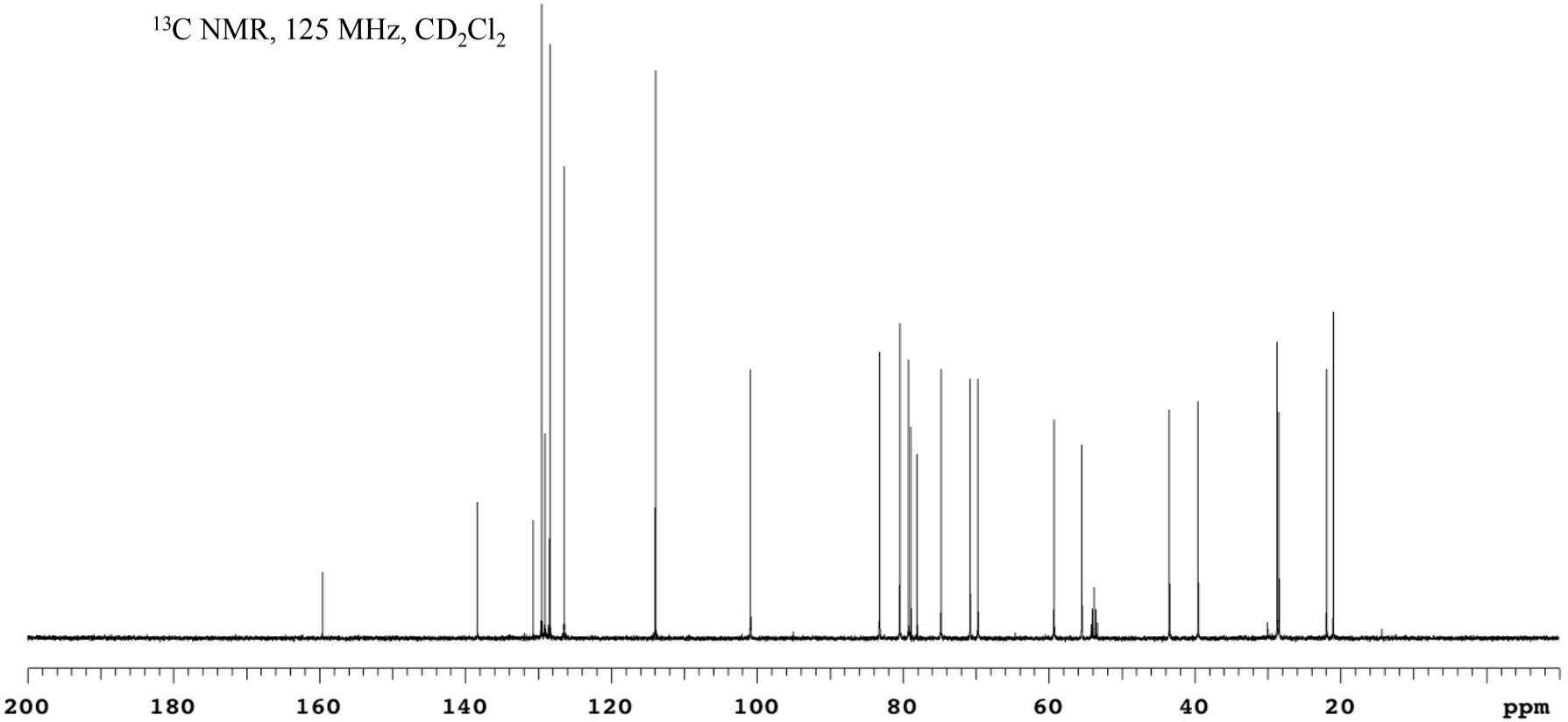
^{1}H NMR, 500 MHz, CD_2Cl_2

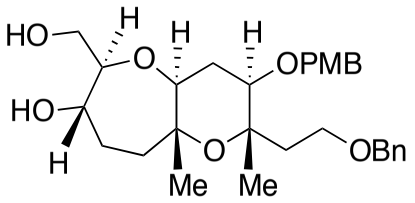




3.93

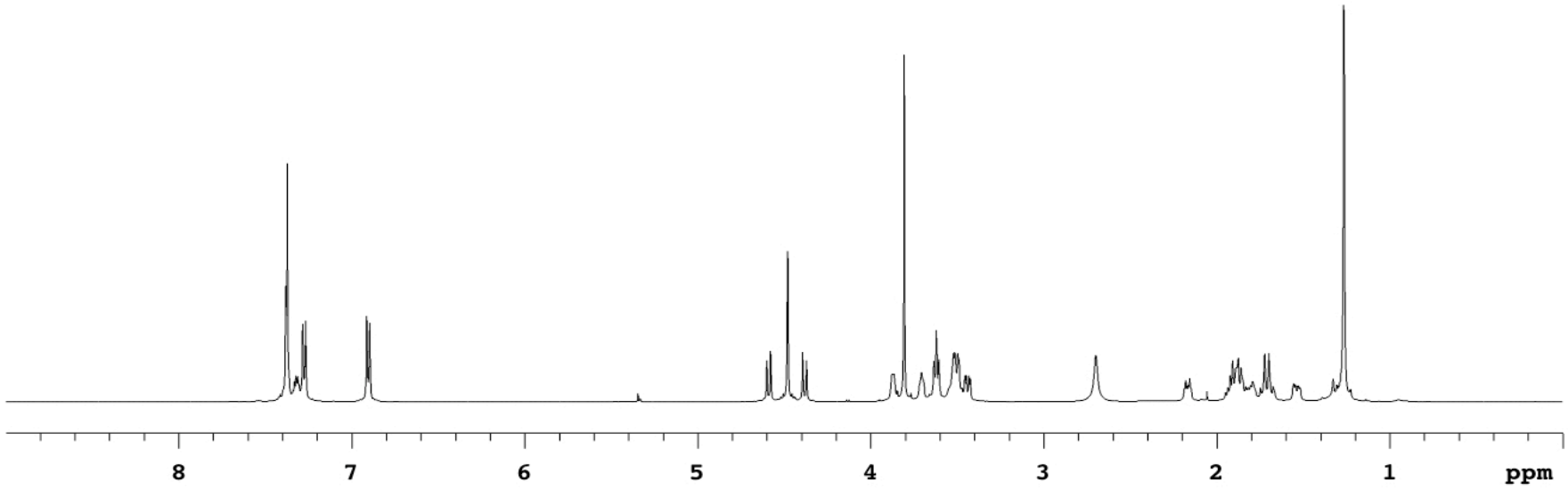
^{13}C NMR, 125 MHz, CD_2Cl_2

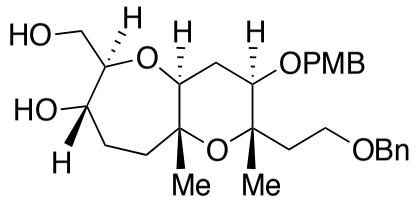




3.94

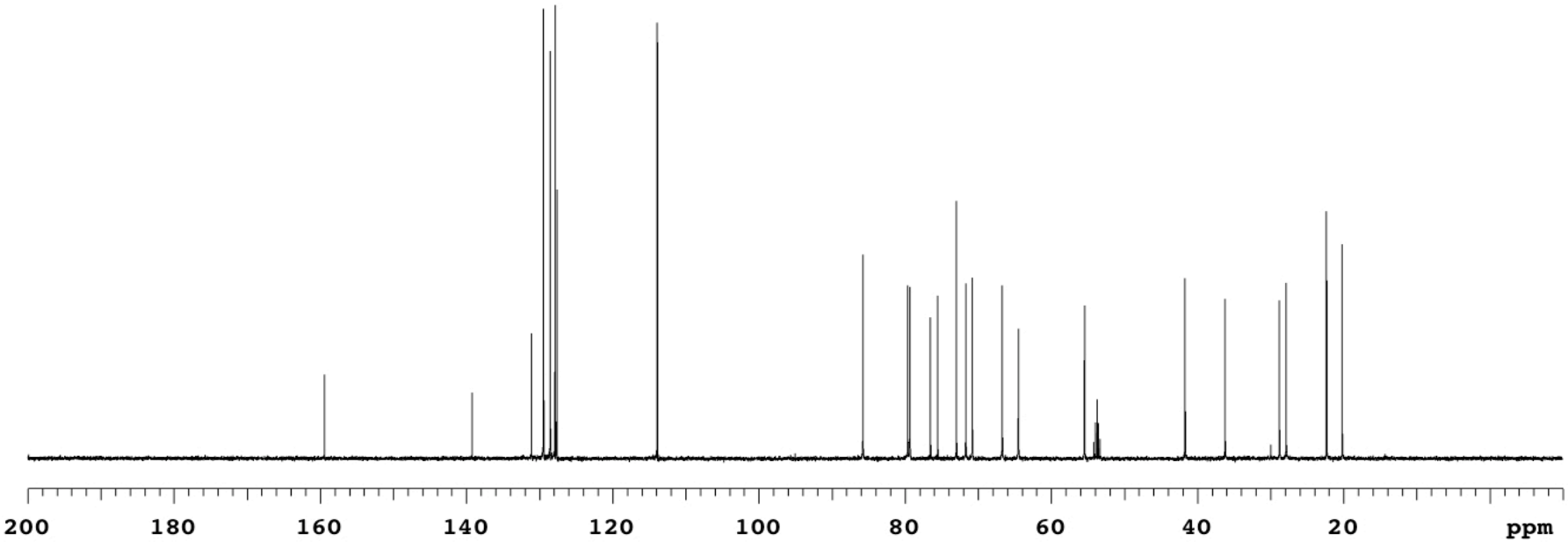
^{1}H NMR, 500 MHz, CD_2Cl_2

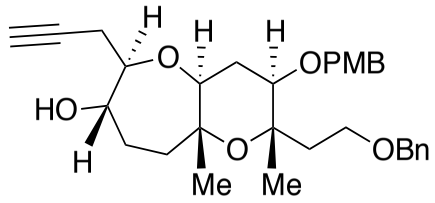




3.94

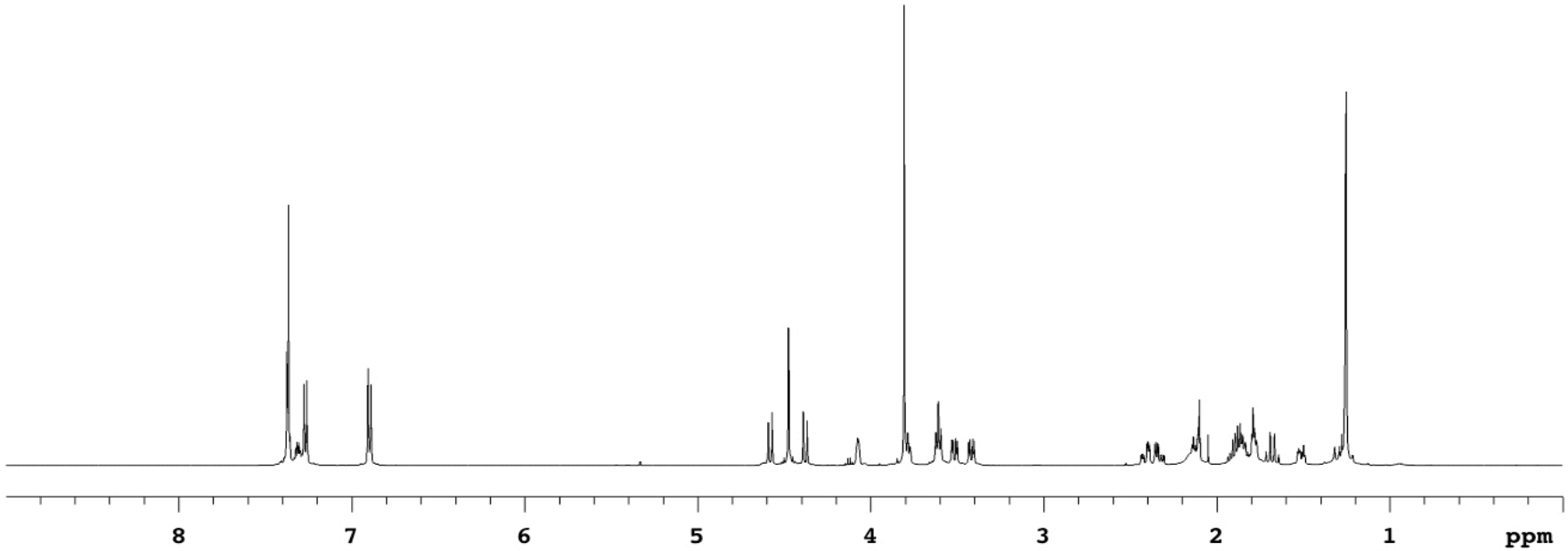
^{13}C NMR, 125 MHz, CD_2Cl_2

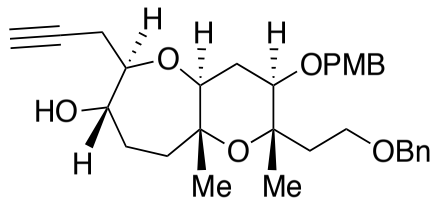




3.97

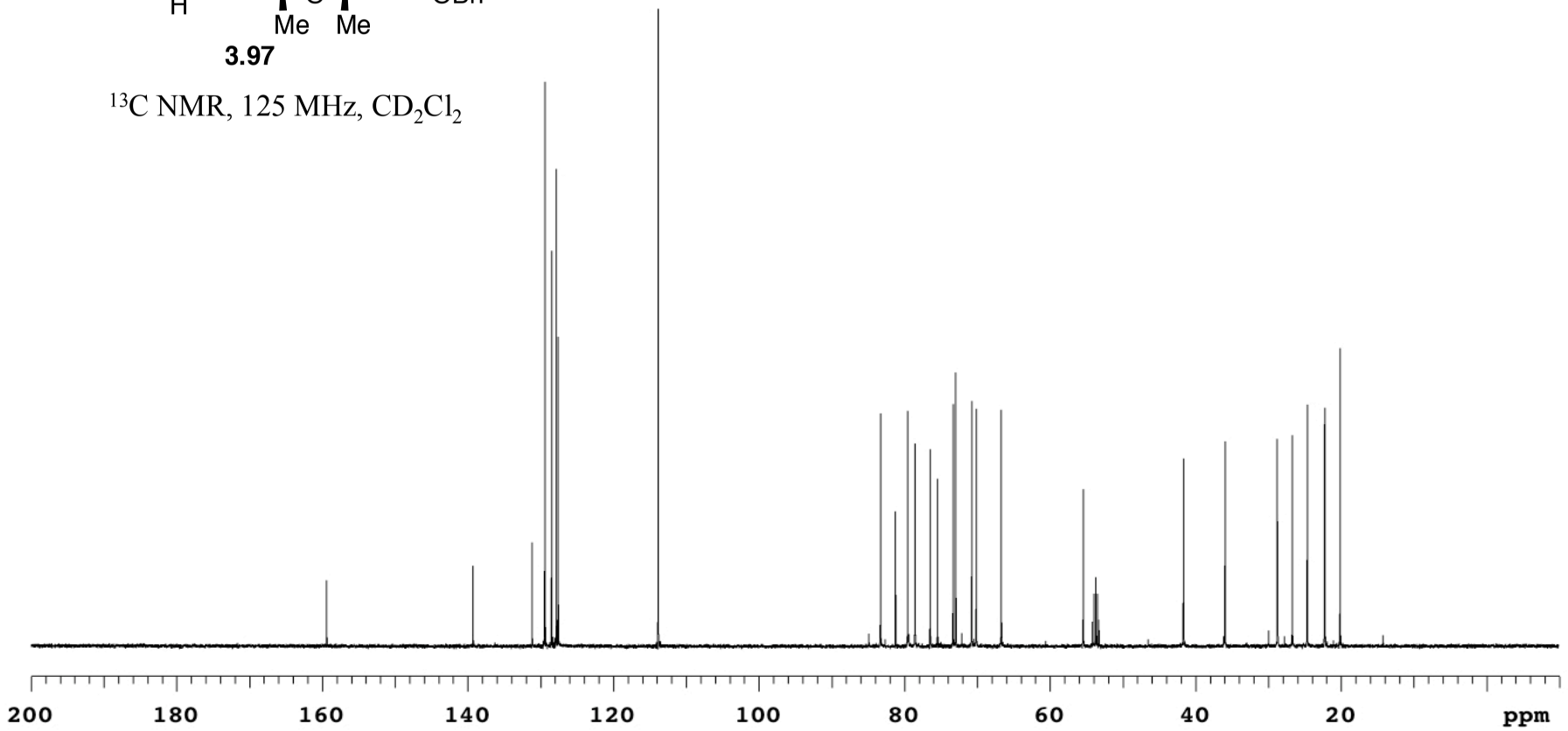
^{1}H NMR, 500 MHz, CD_2Cl_2

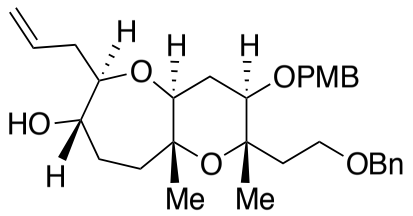




3.97

^{13}C NMR, 125 MHz, CD_2Cl_2





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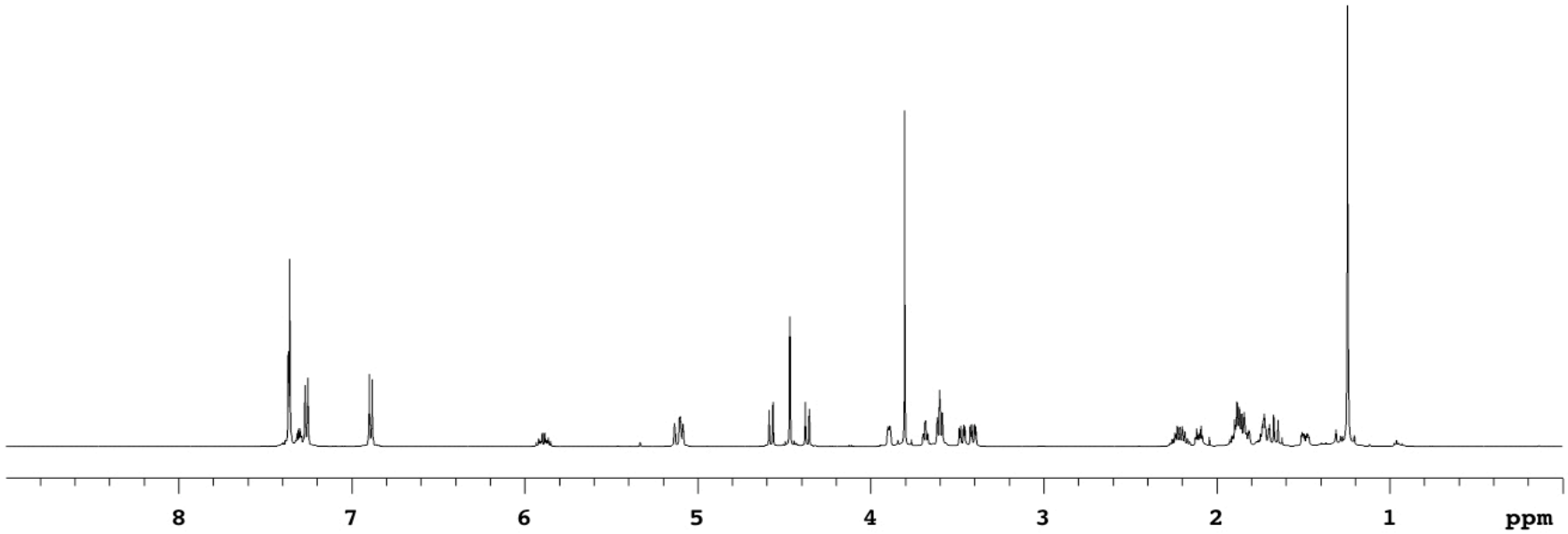
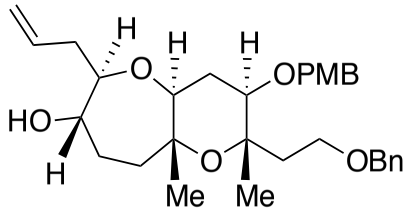
^{1}H NMR, 500 MHz, CD_2Cl_2





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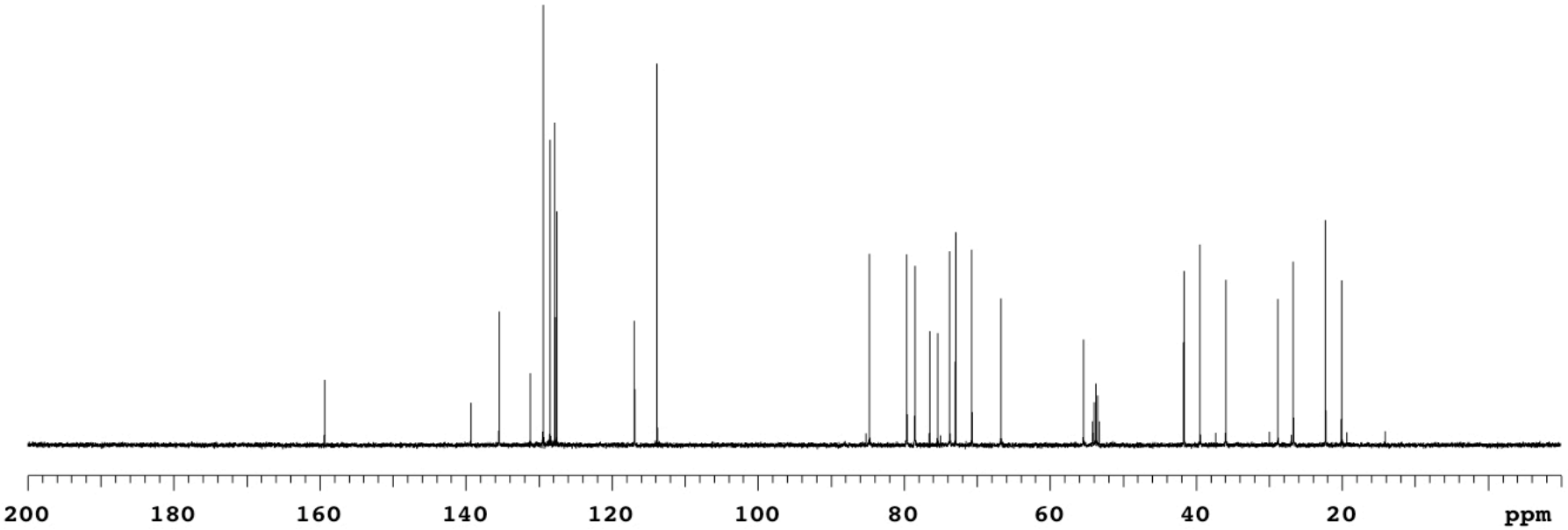
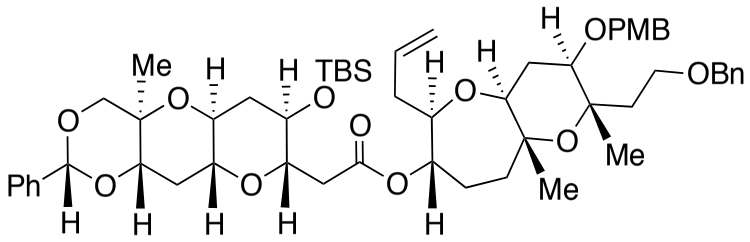
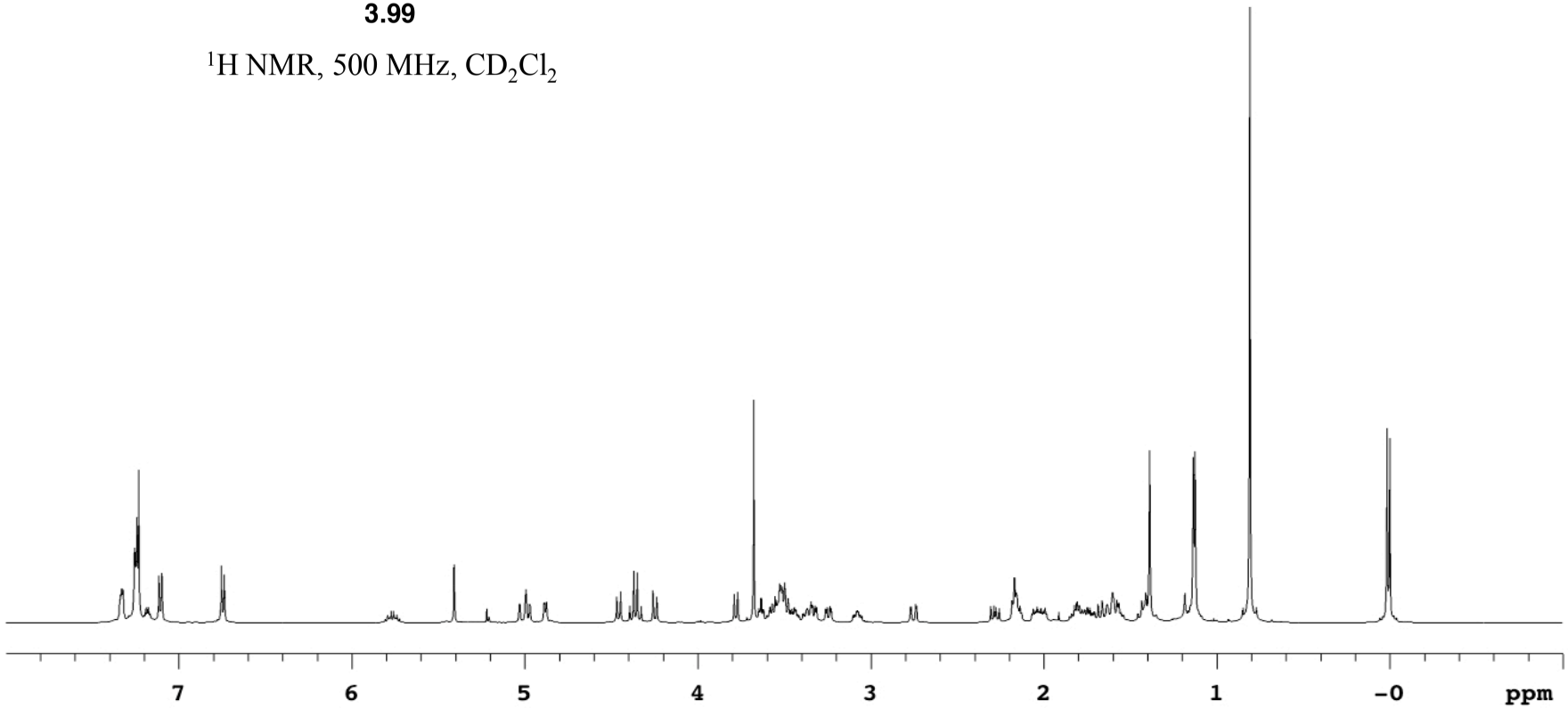
^{13}C NMR, 125 MHz, CD_2Cl_2

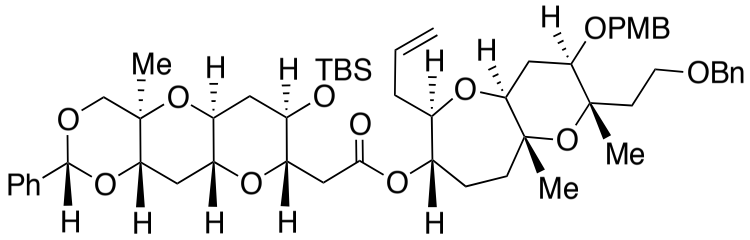




3.99

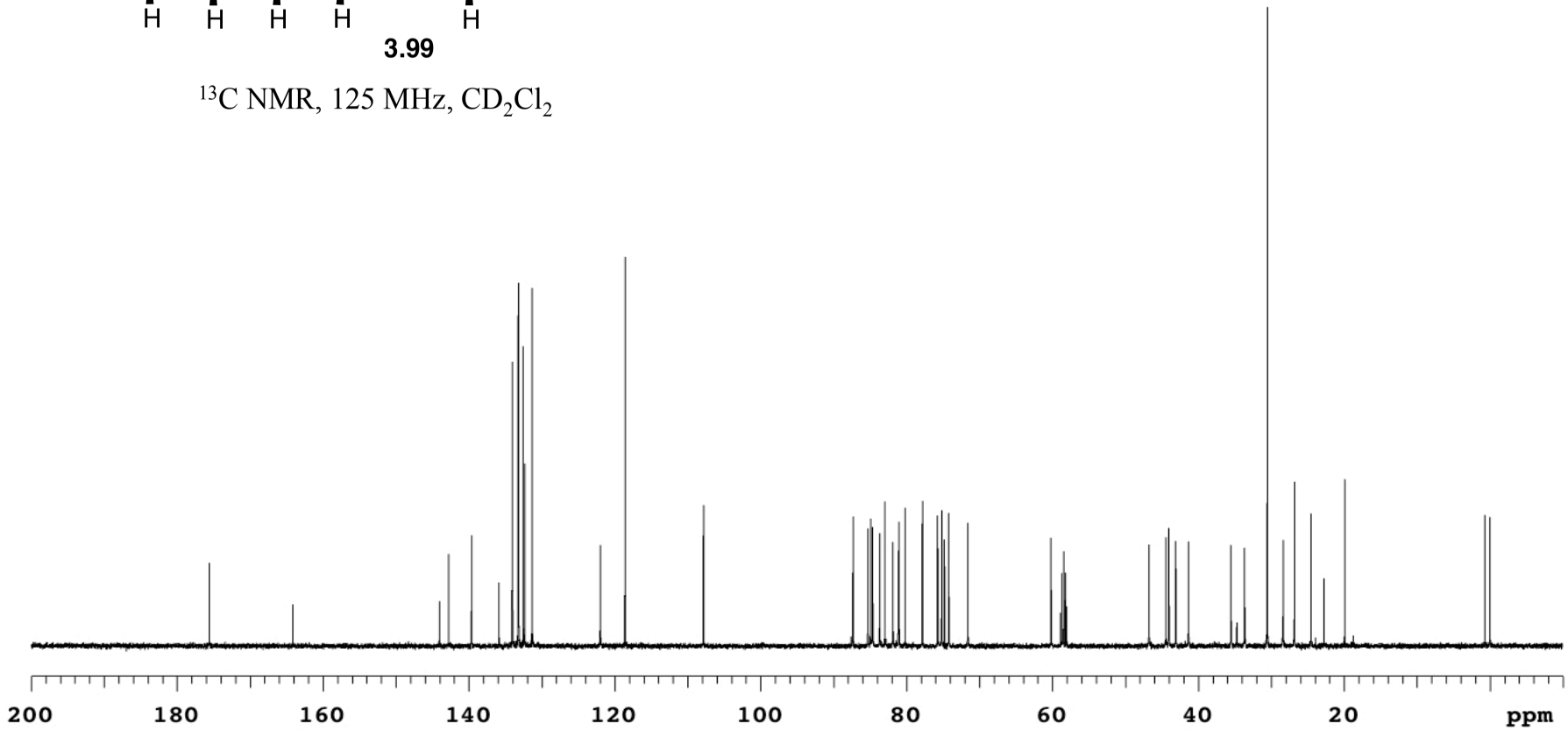
^{1}H NMR, 500 MHz, CD_2Cl_2

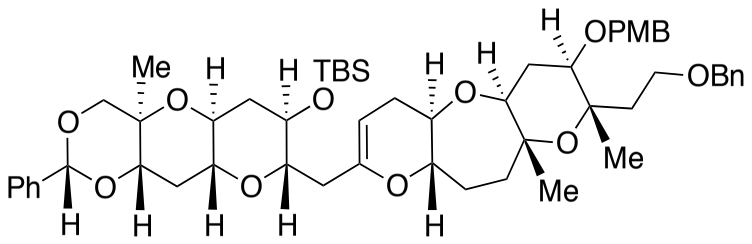




3.99

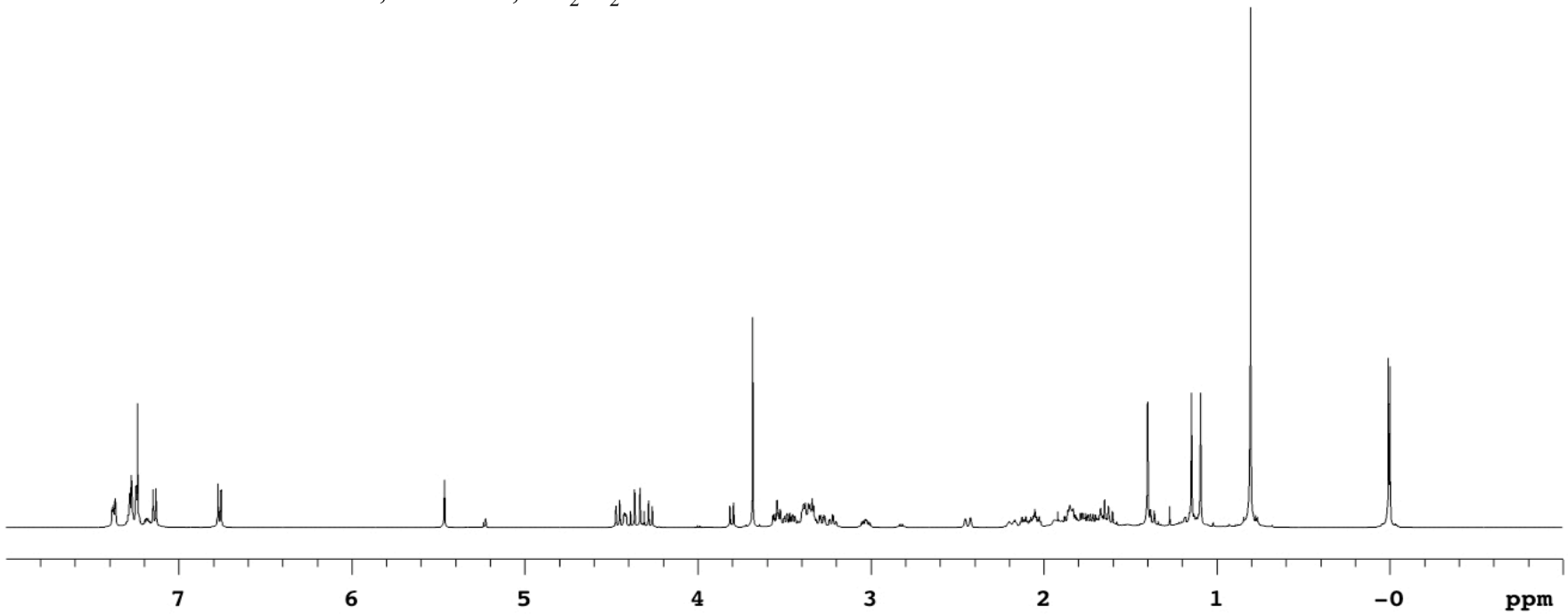
^{13}C NMR, 125 MHz, CD_2Cl_2

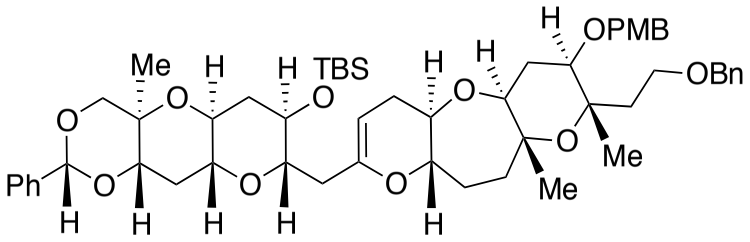




3.100

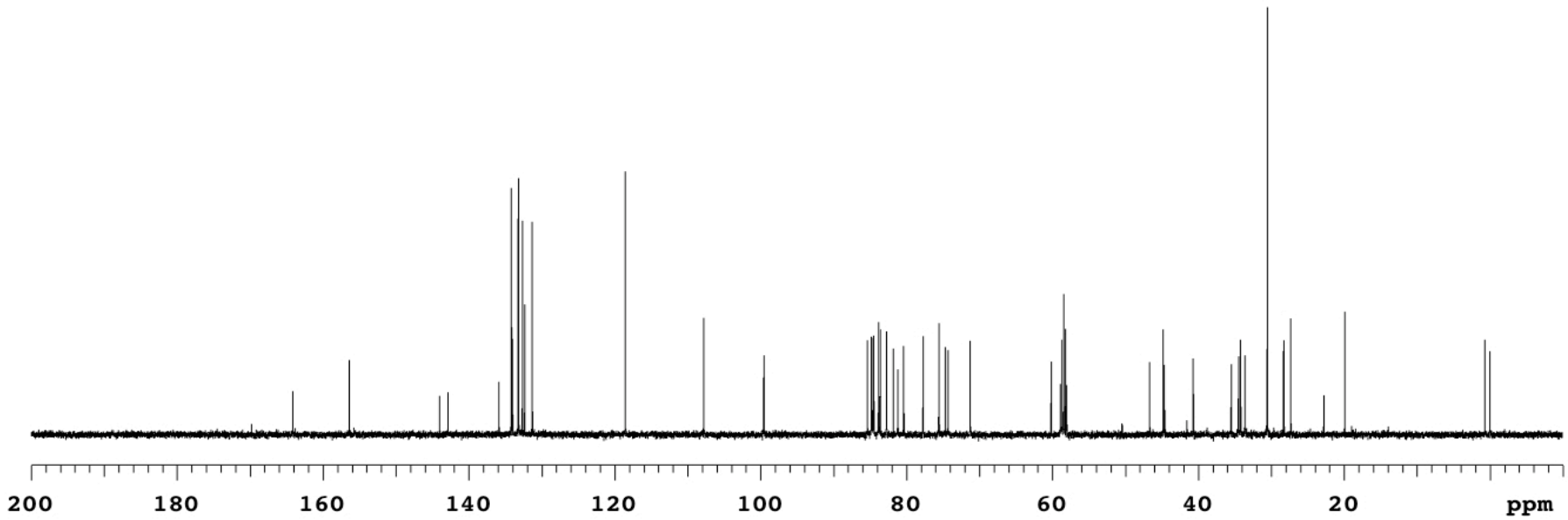
^{1}H NMR, 500 MHz, CD_2Cl_2

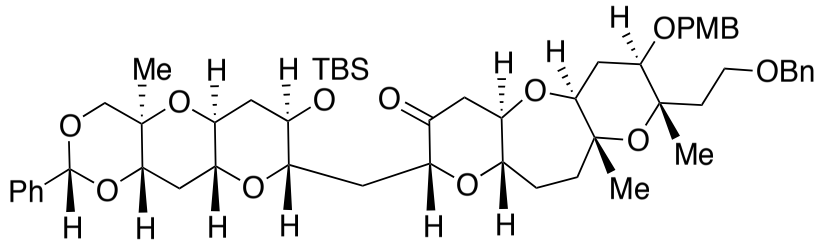




3.100

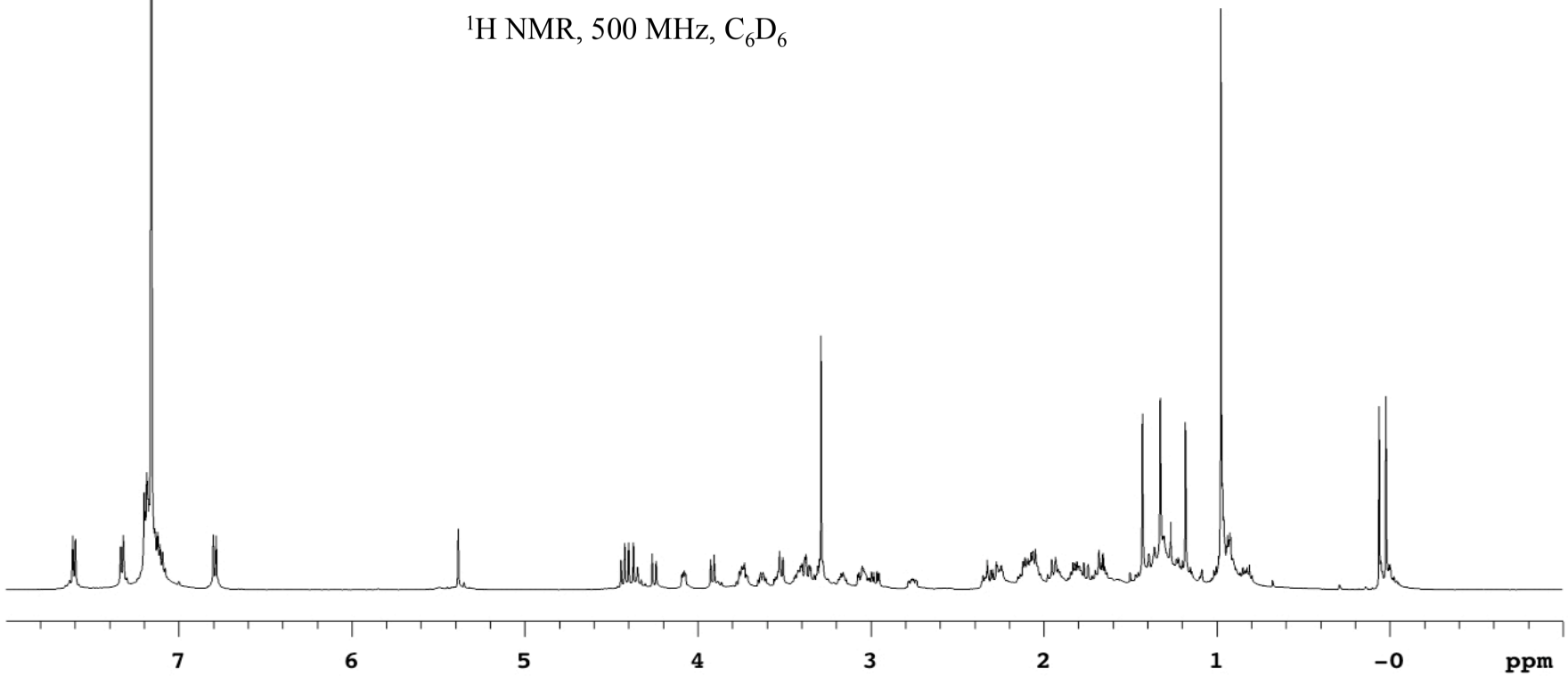
^{13}C NMR, 125 MHz, CD_2Cl_2

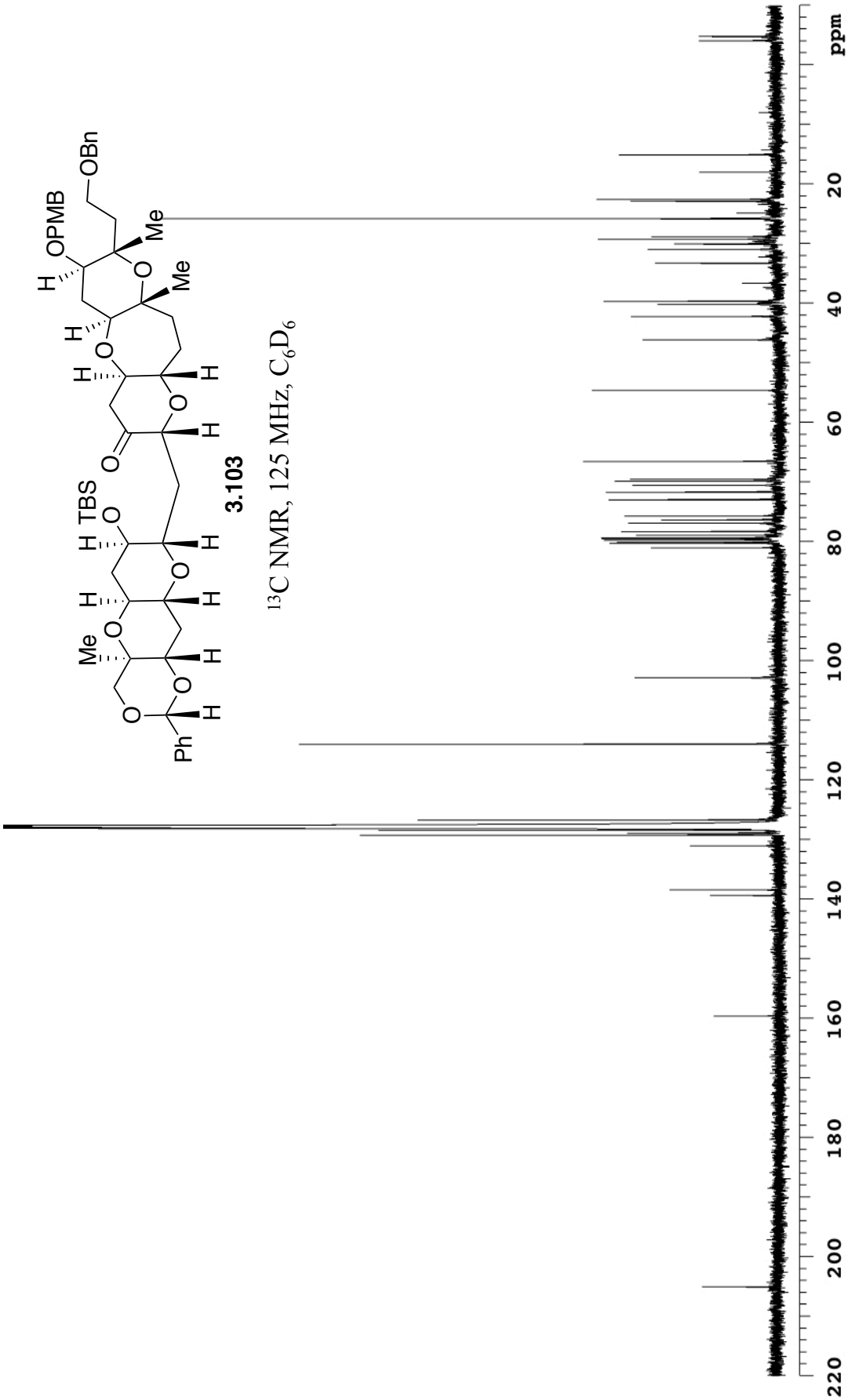




3.103

^{1}H NMR, 500 MHz, C_6D_6

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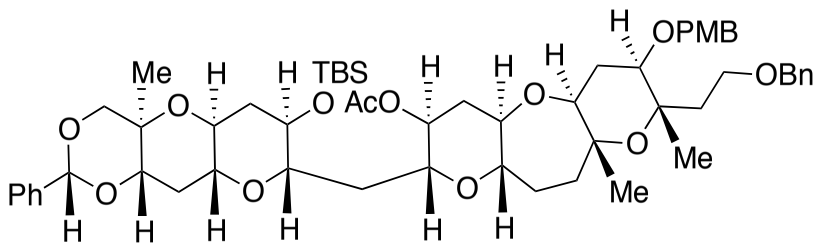
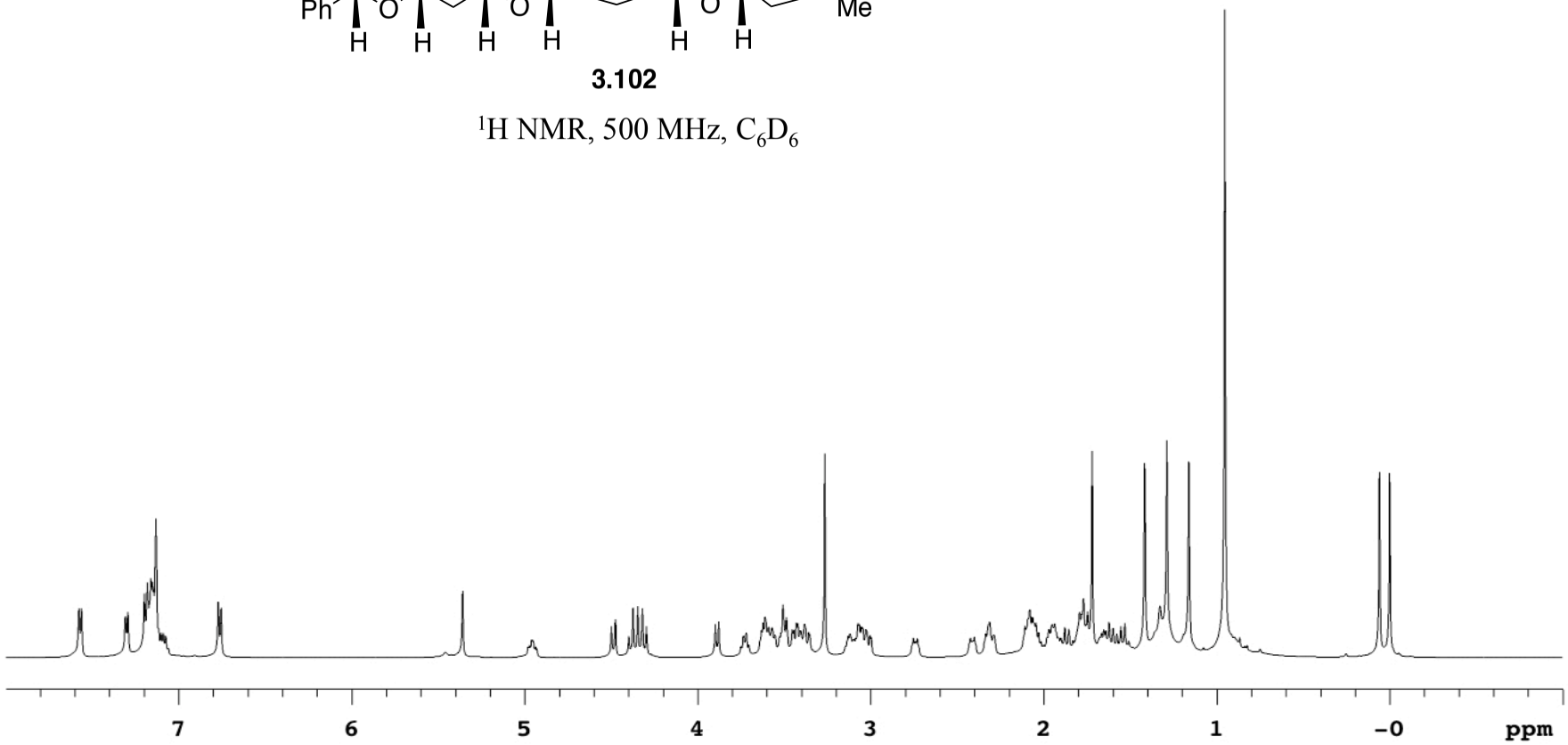
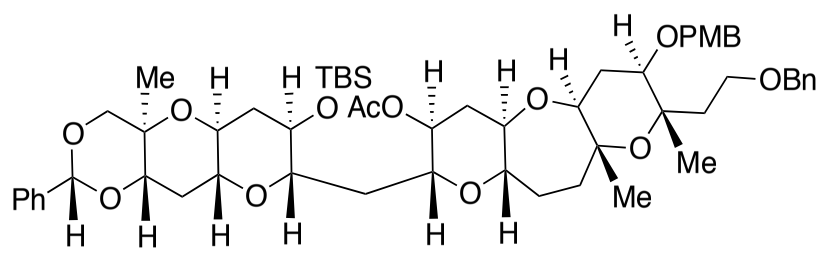
Ph
3.103
^{13}C NMR, 125 MHz, C_6D_6
ppm
220
200
180
160
140
120
100
80
60
40
20



3.102

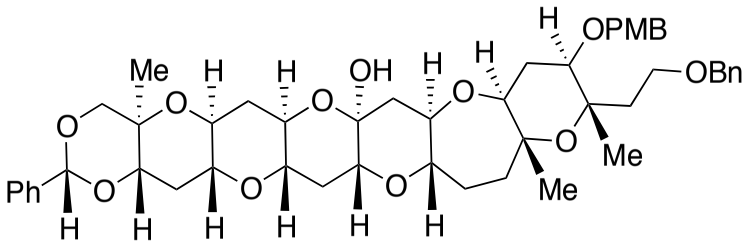
^{1}H NMR, 500 MHz, C_6D_6





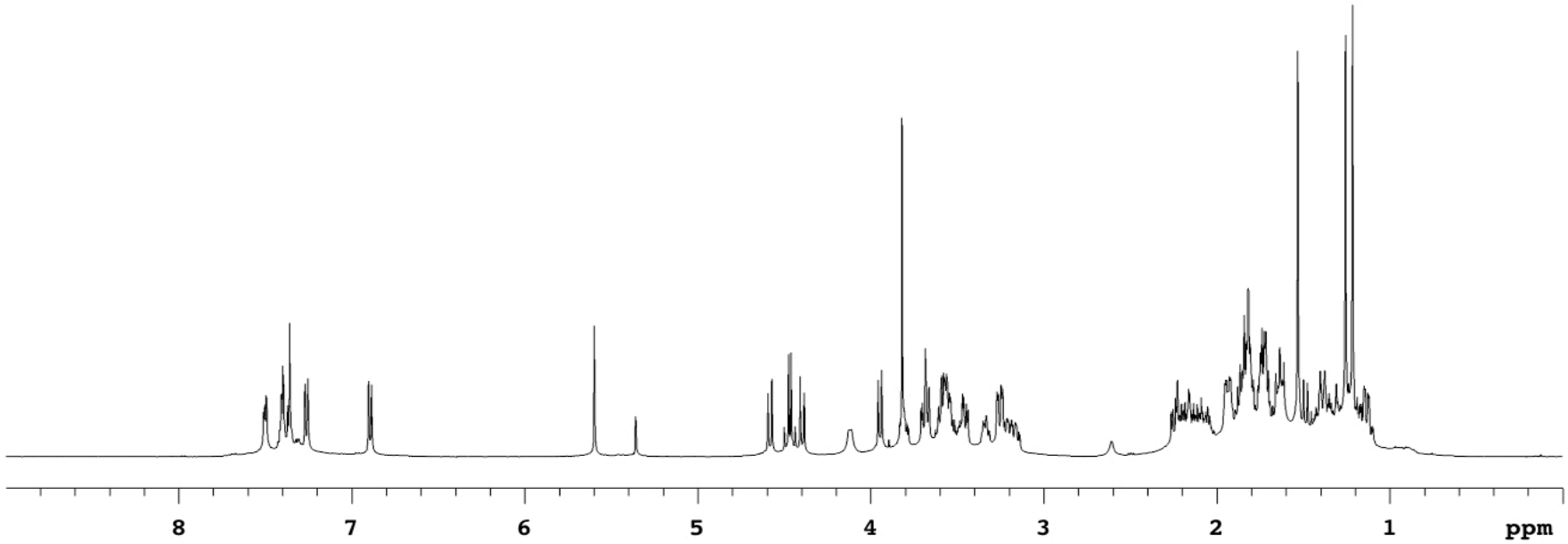
3.102

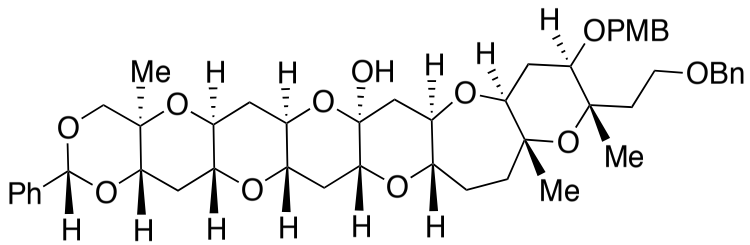
^{13}C NMR, 125 MHz, C_6D_6



3.104

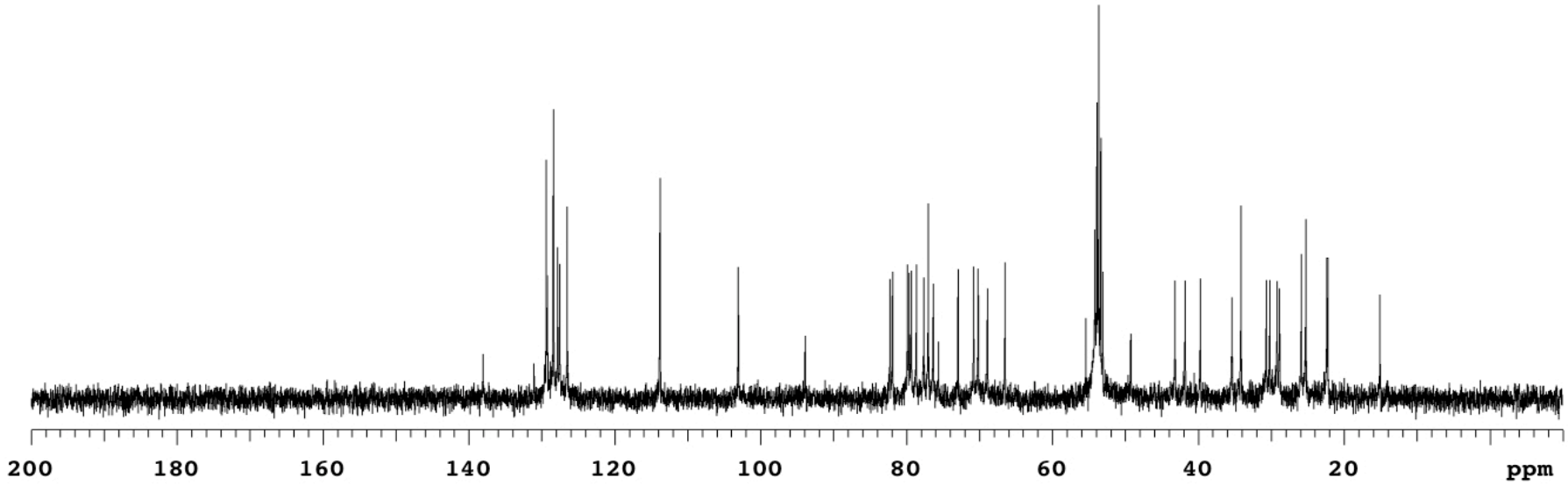
^{1}H NMR, 500 MHz, CD_2Cl_2

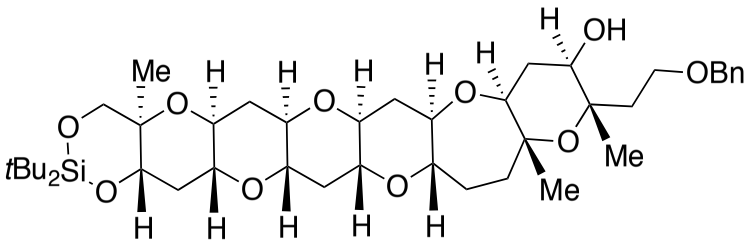




3.104

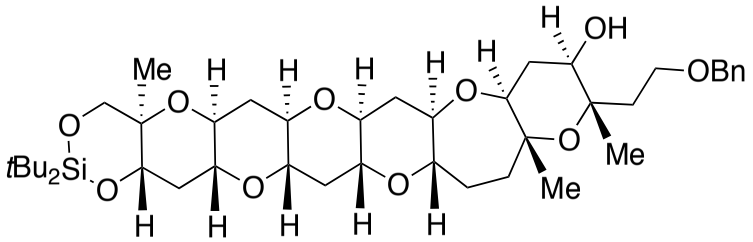
^{13}C NMR, 125 MHz, CD_2Cl_2





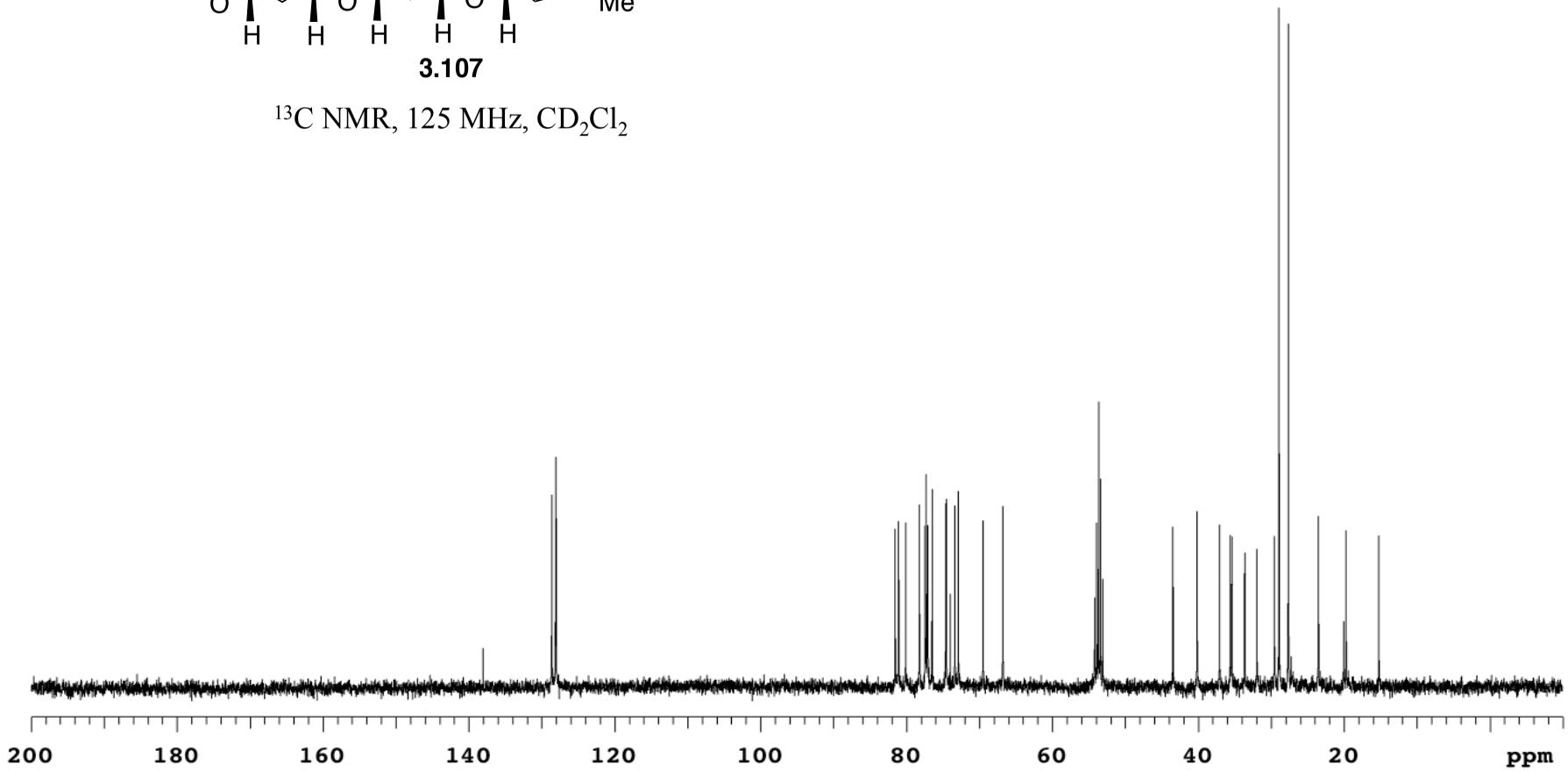
3.107

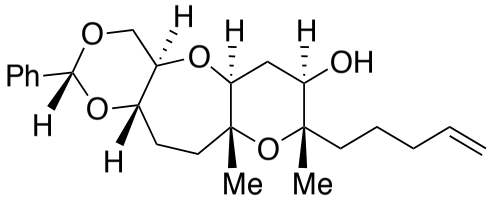
^{1}H NMR, 500 MHz, CD_2Cl_2



3.107

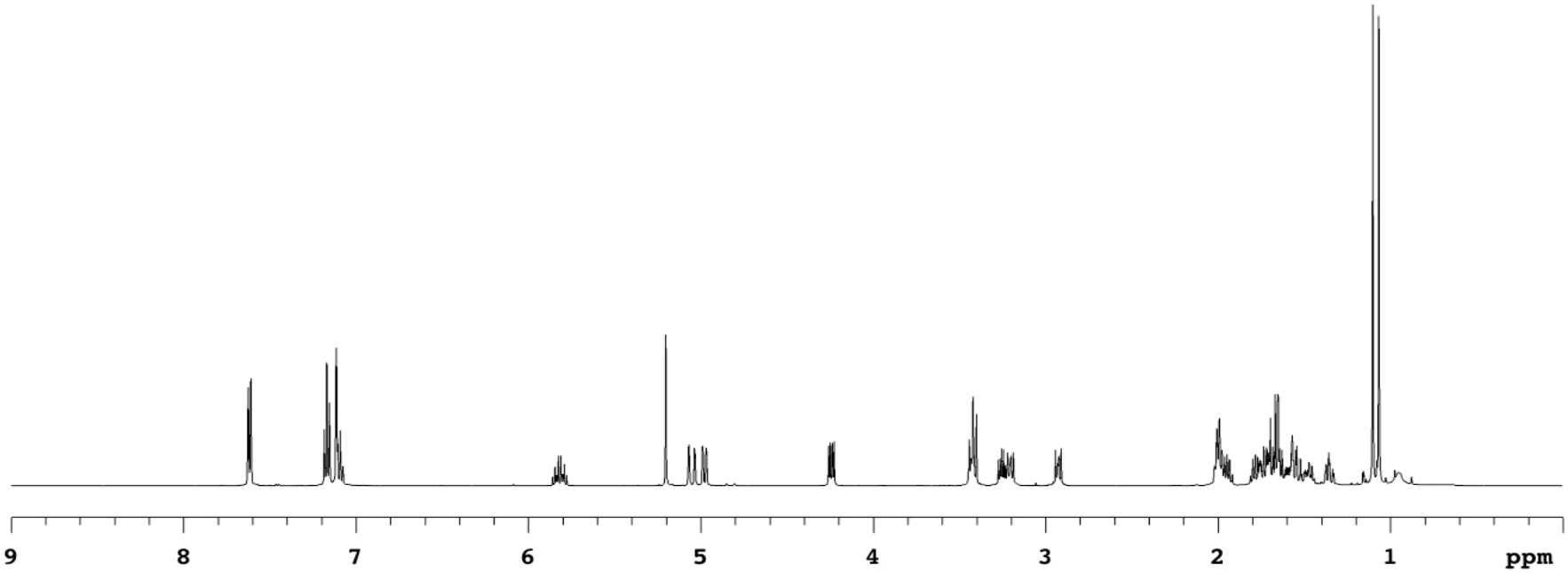
^{13}C NMR, 125 MHz, CD_2Cl_2

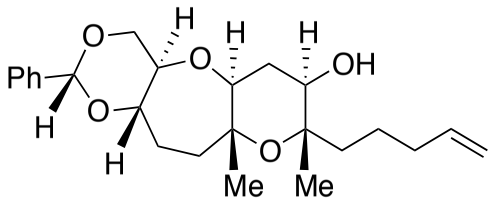




3.112

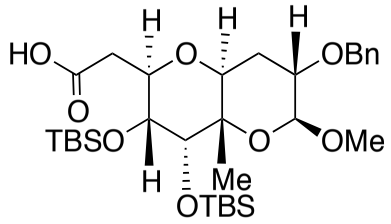
^{1}H NMR, 500 MHz, C_6D_6





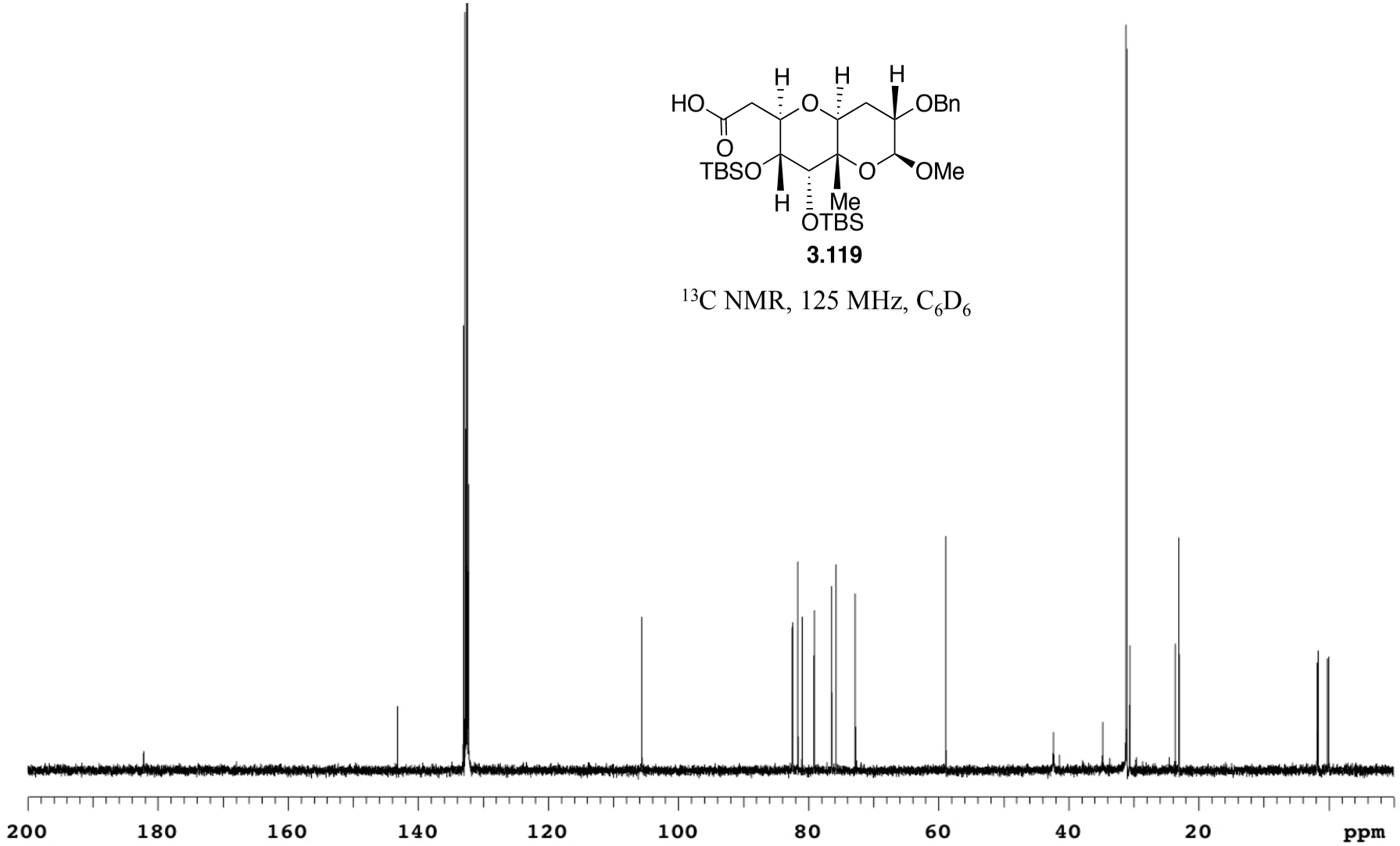
3.112

^{13}C NMR, 125 MHz, C_6D_6



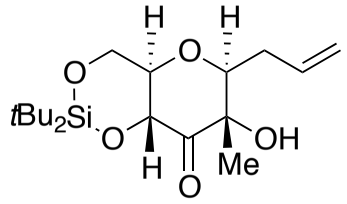
3.119

^{1}H NMR, 500 MHz, C_6D_6



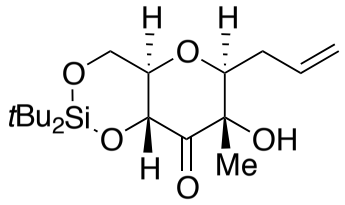
3.119

^{13}C NMR, 125 MHz, C_6D_6



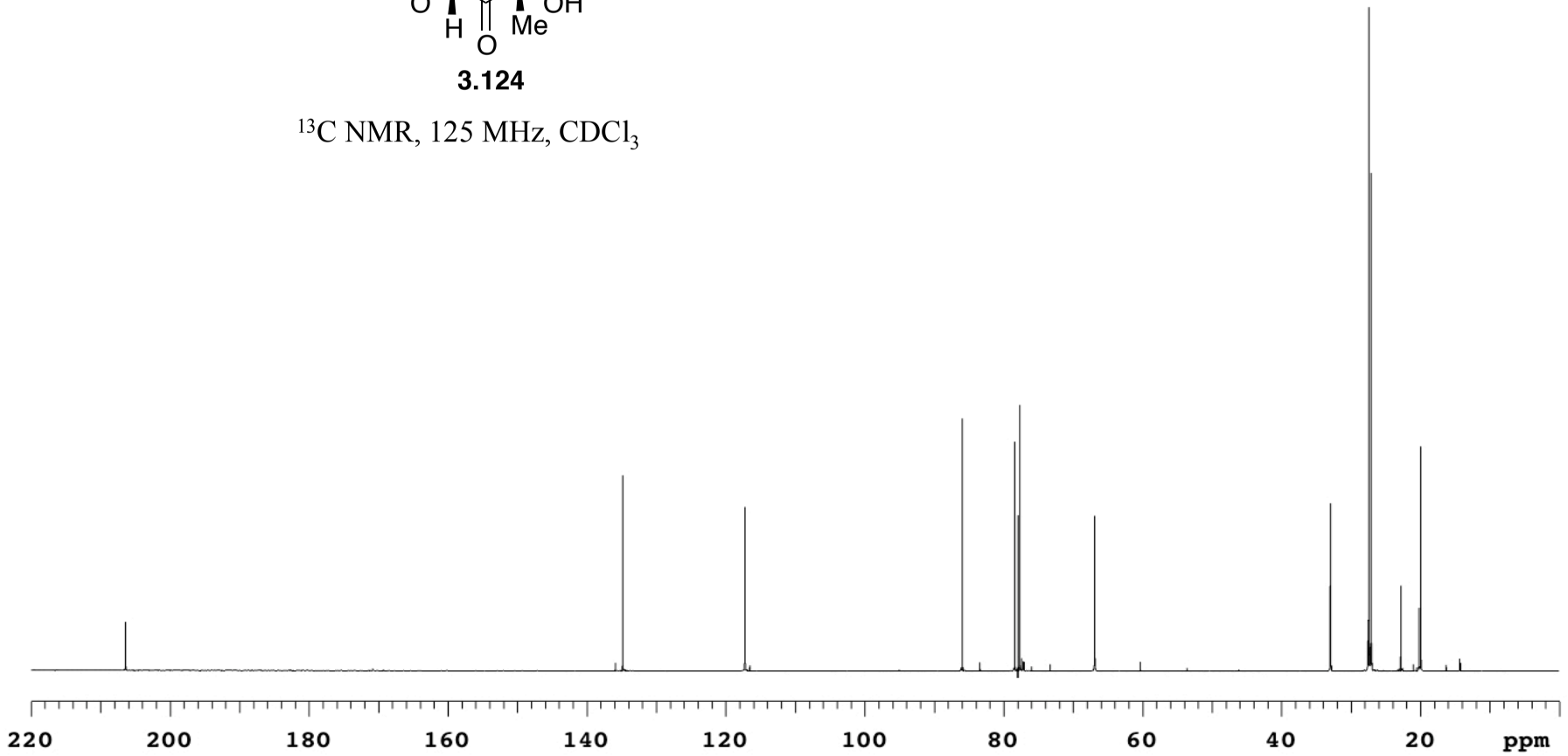
3.124

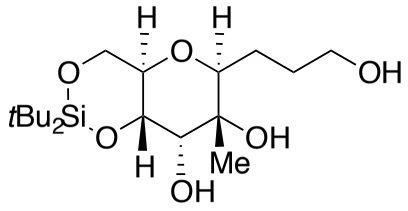
^{1}H NMR, 500 MHz, $CDCl_3$



3.124

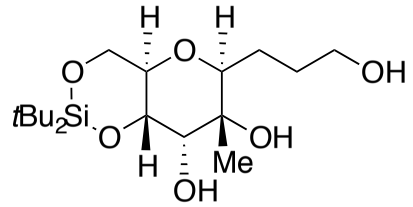
^{13}C NMR, 125 MHz, $CDCl_3$





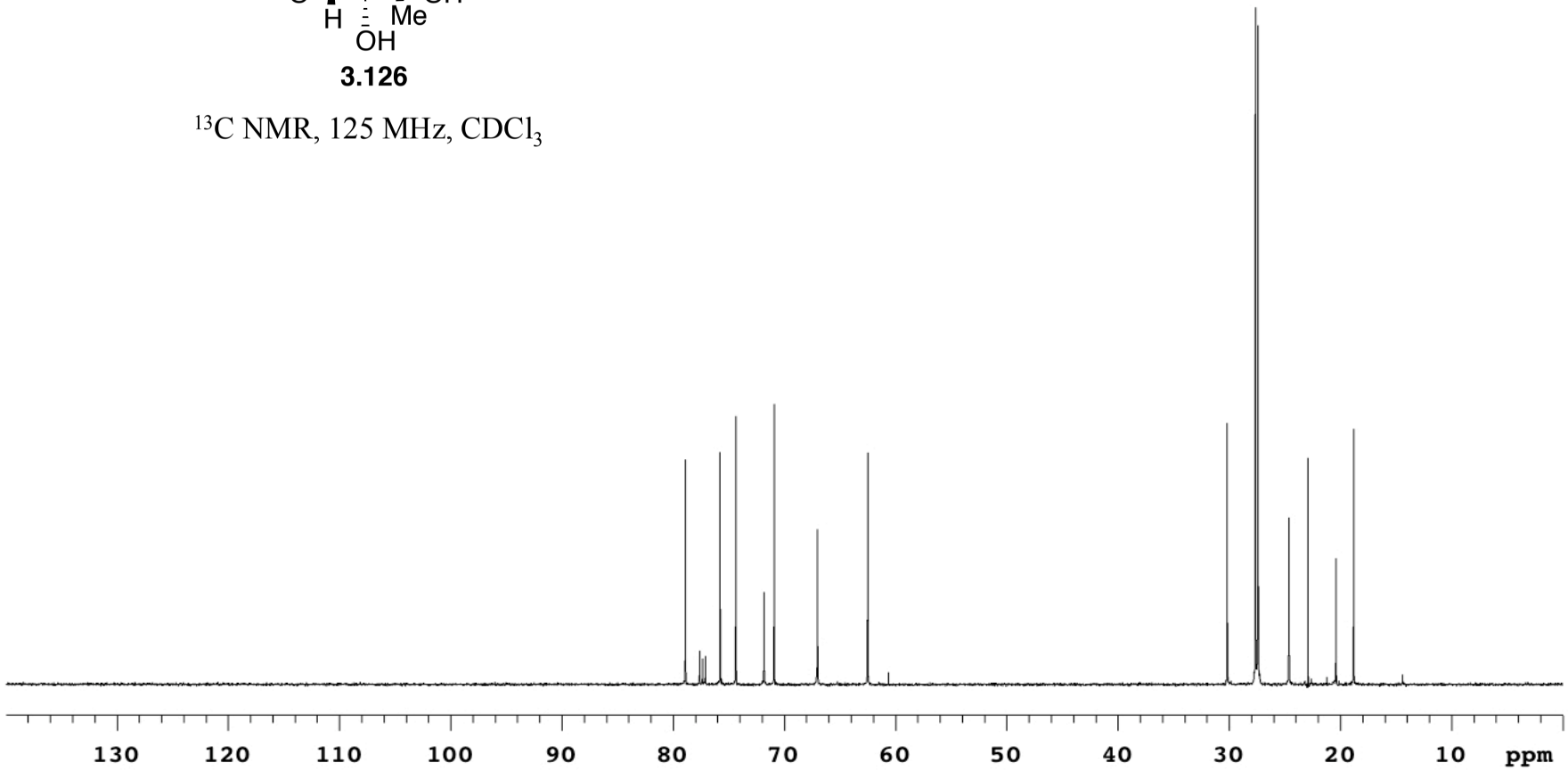
3.126

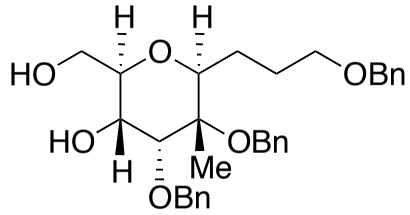
^{1}H NMR, 500 MHz, $CDCl_3$



3.126

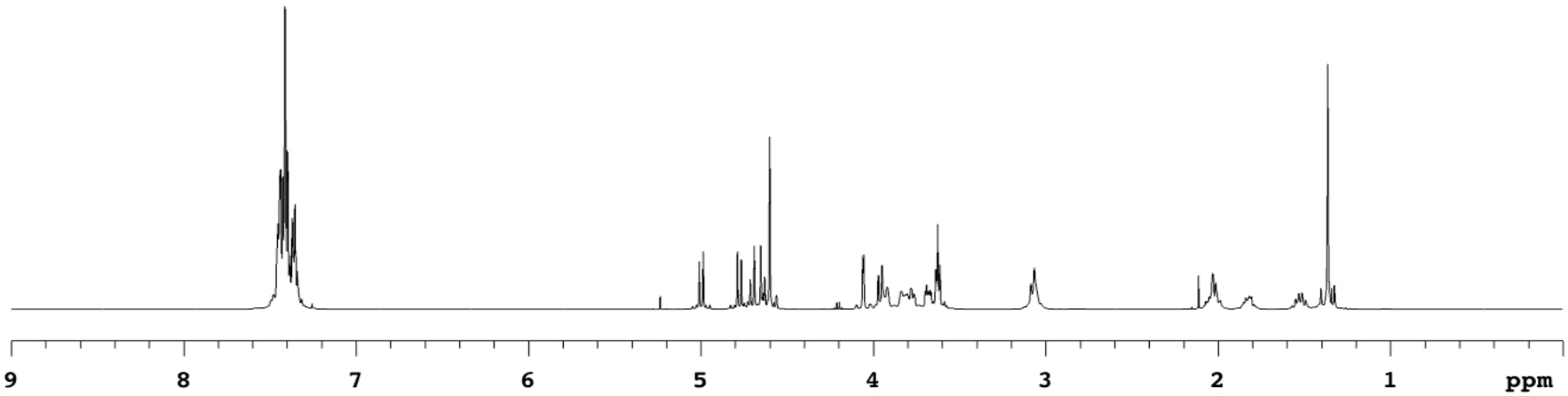
^{13}C NMR, 125 MHz, $CDCl_3$

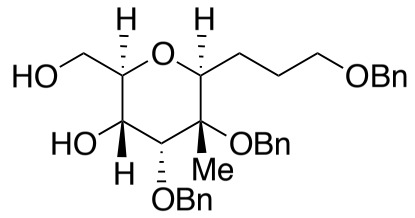




3.127

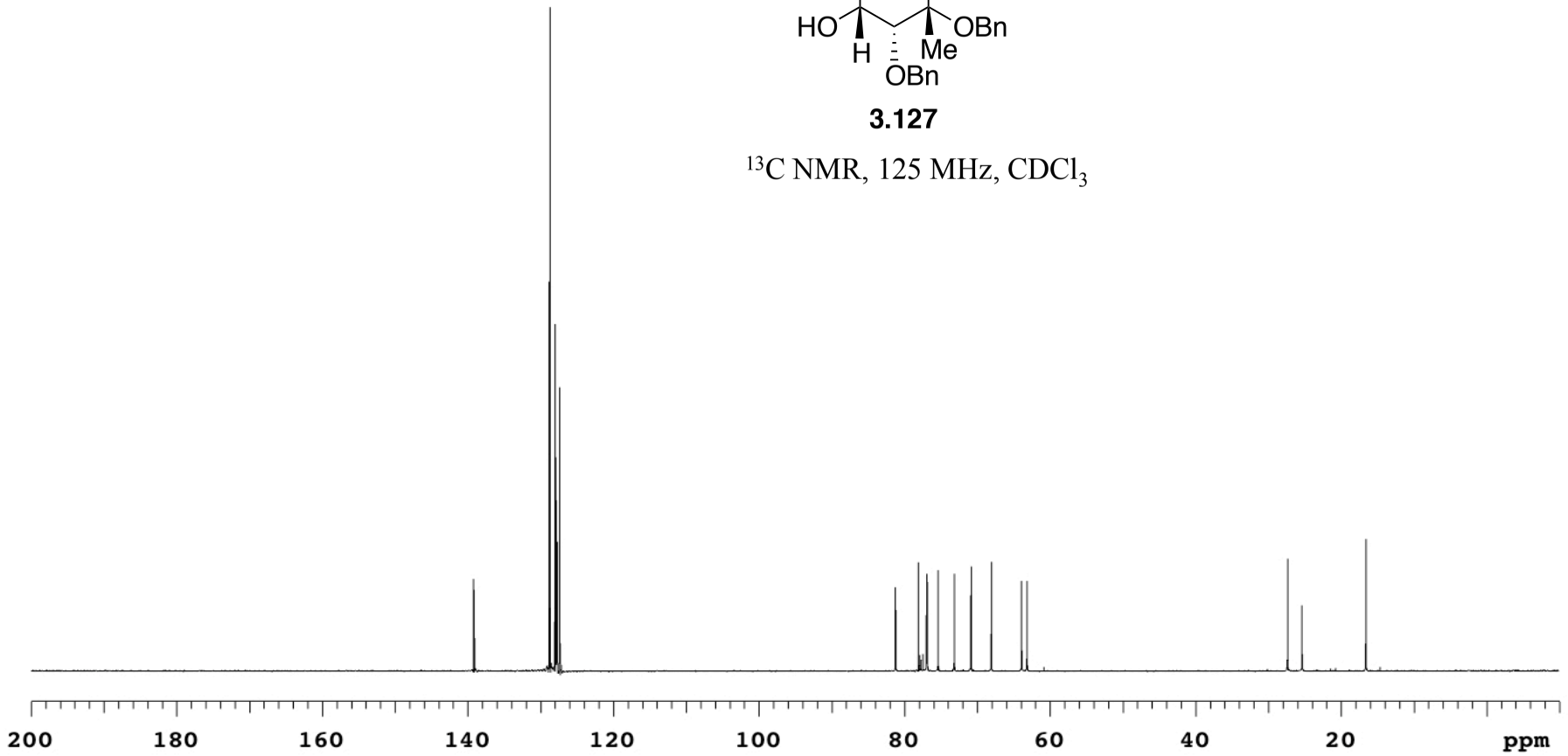
^{1}H NMR, 500 MHz, $CDCl_3$

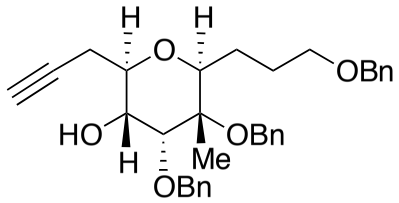




3.127

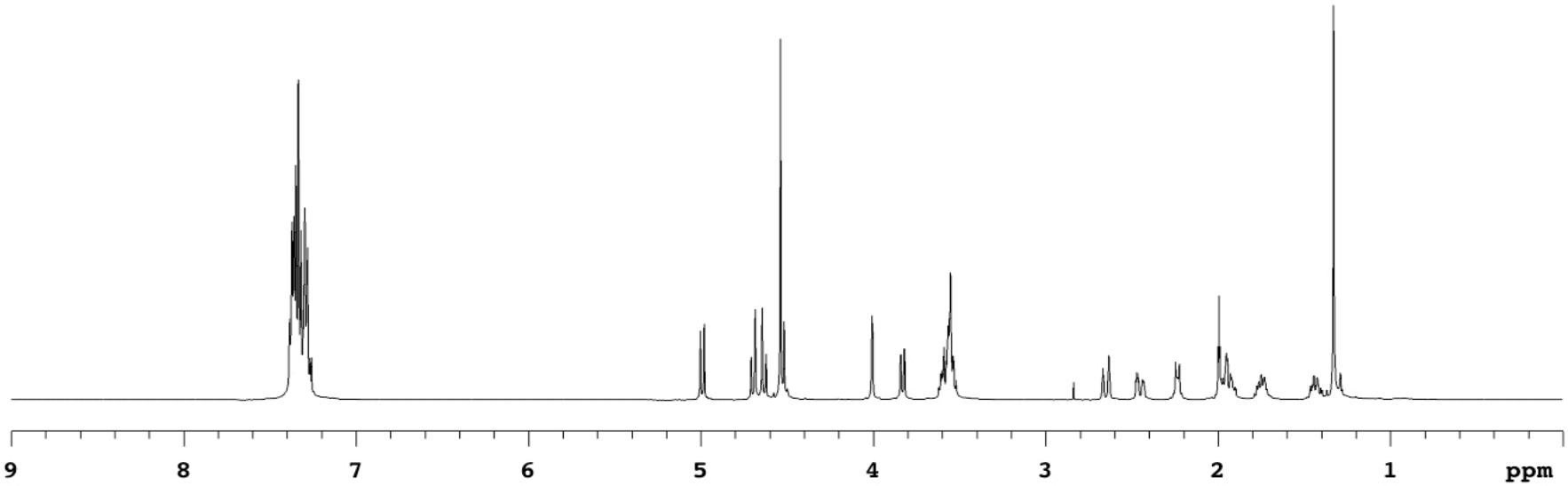
^{13}C NMR, 125 MHz, $CDCl_3$

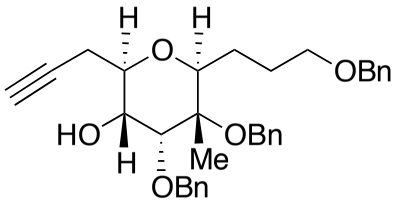




3.129

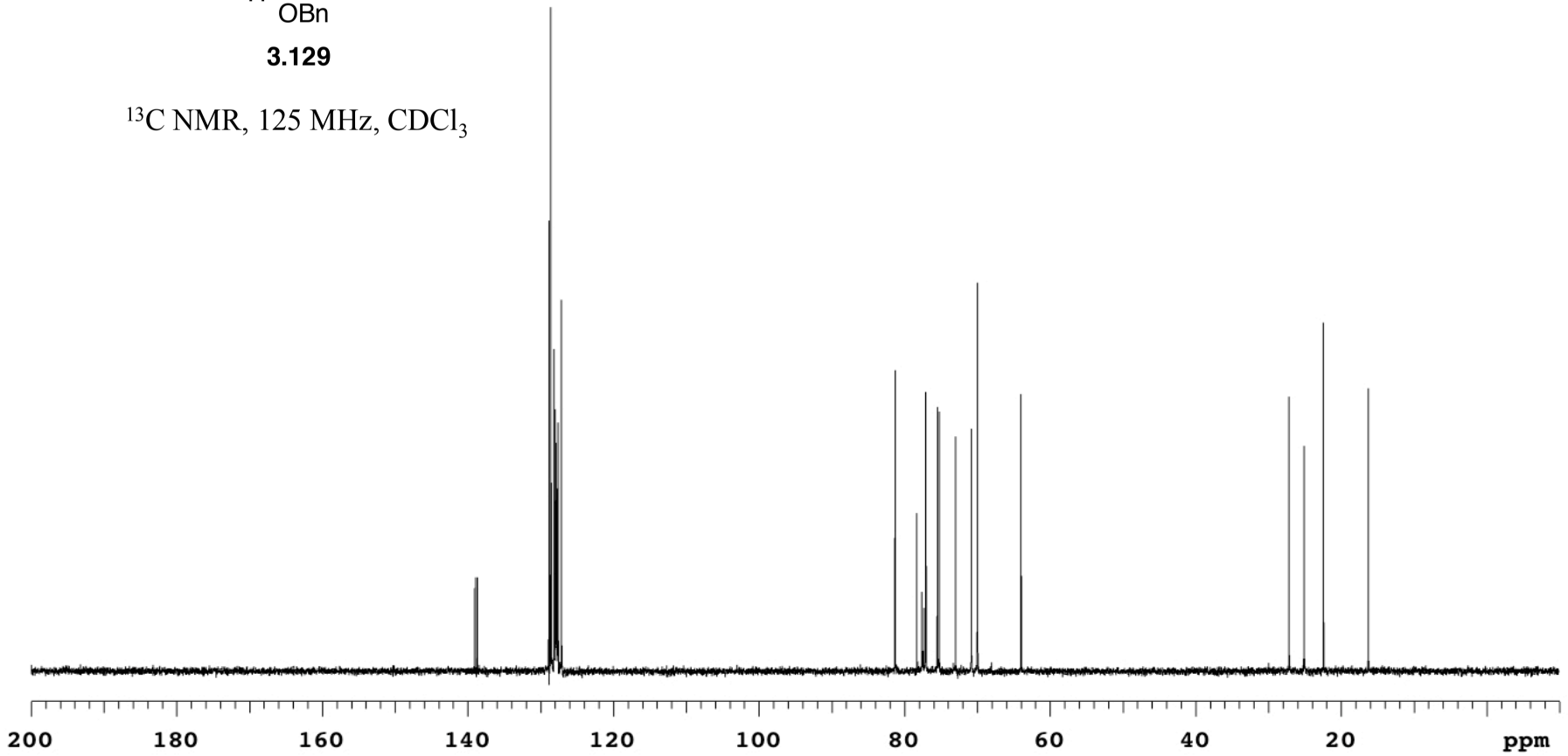
^{1}H NMR, 500 MHz, $CDCl_3$

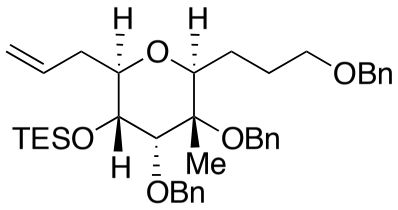




3.129

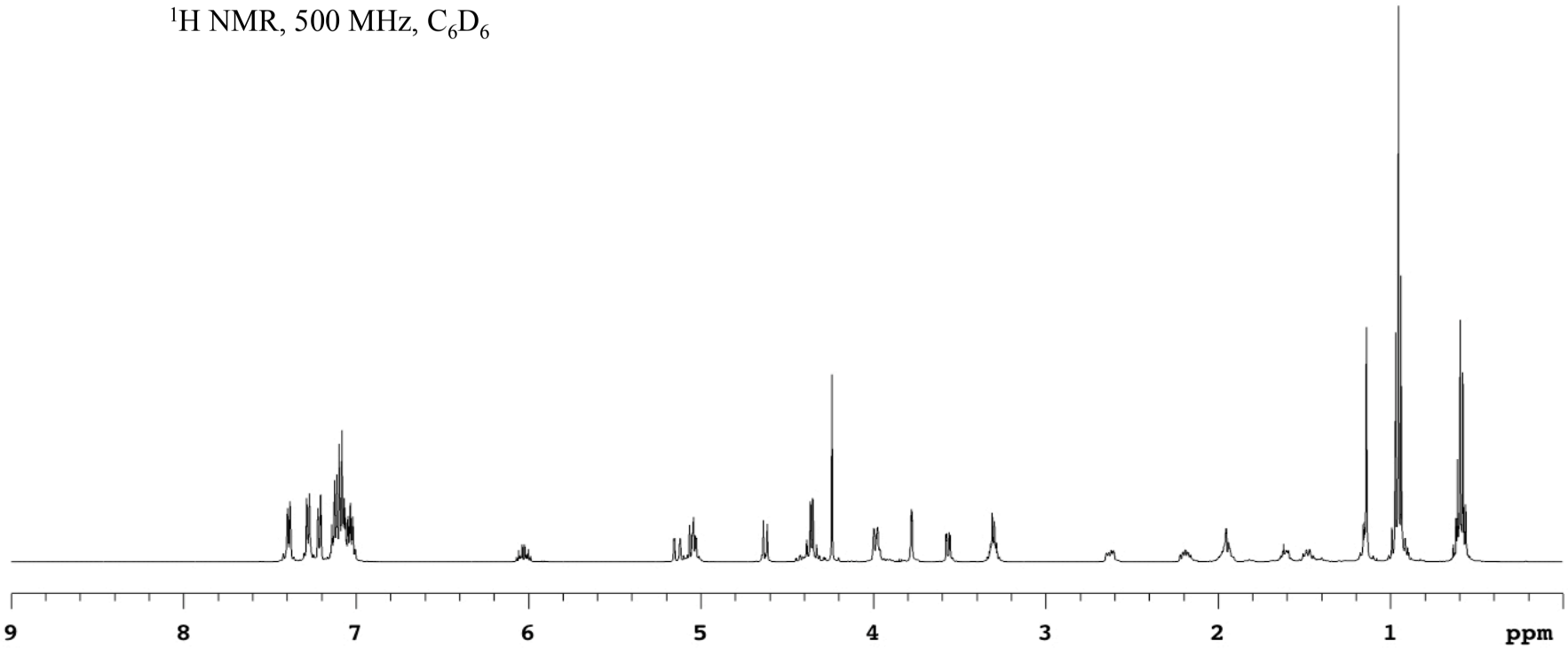
^{13}C NMR, 125 MHz, $CDCl_3$

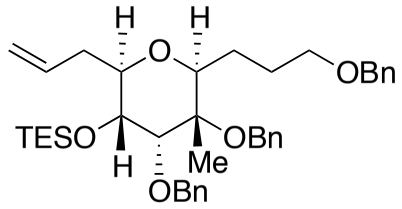




3.130

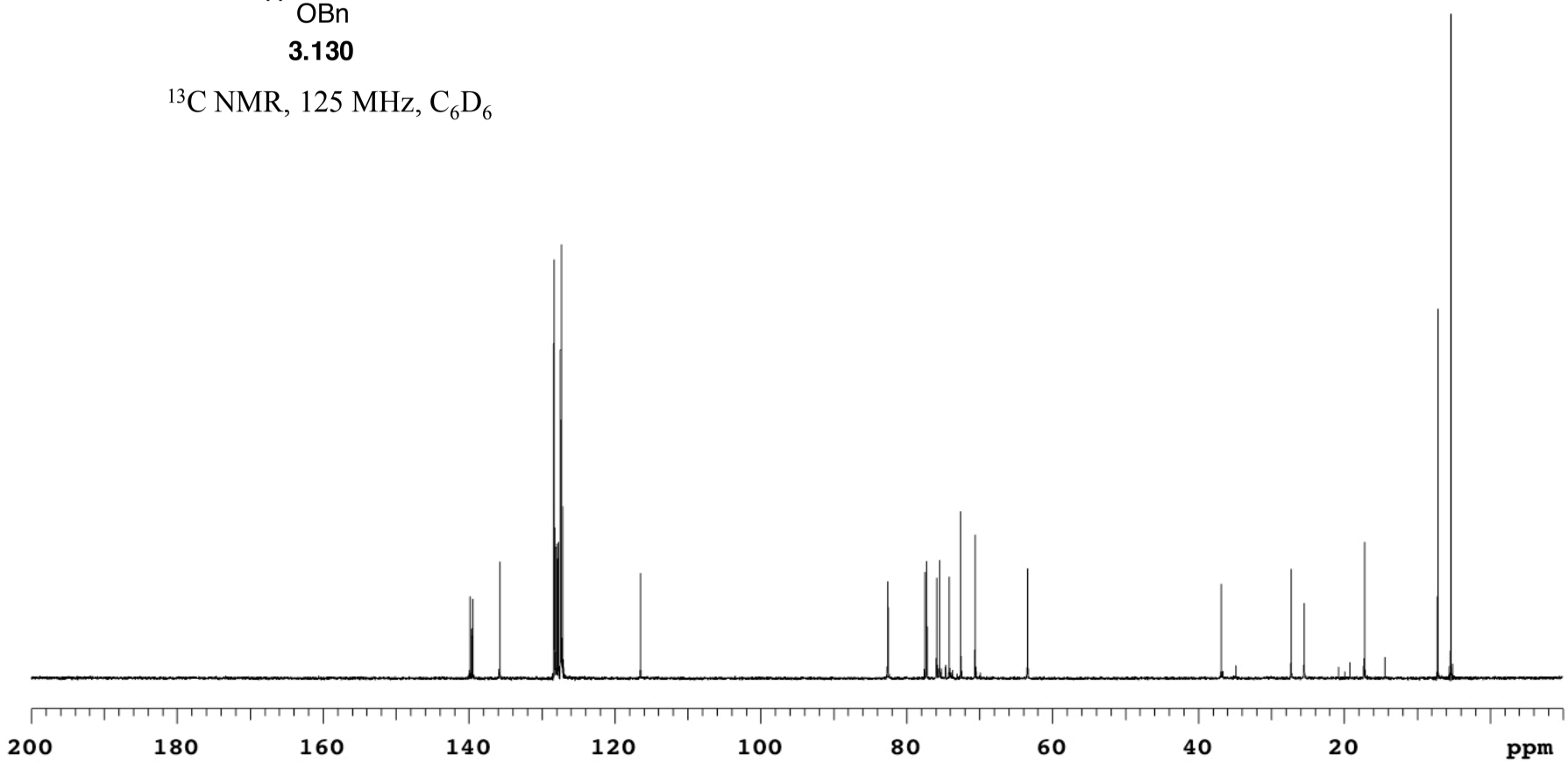
^{1}H NMR, 500 MHz, C_6D_6

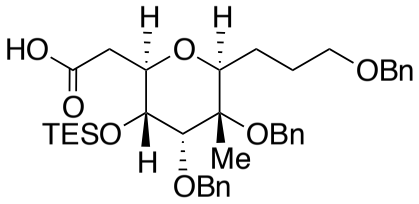




3.130

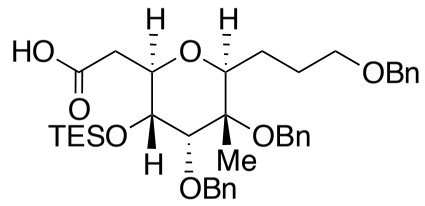
^{13}C NMR, 125 MHz, C_6D_6





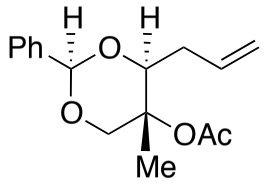
3.131

^{1}H NMR, 500 MHz, C_6D_6



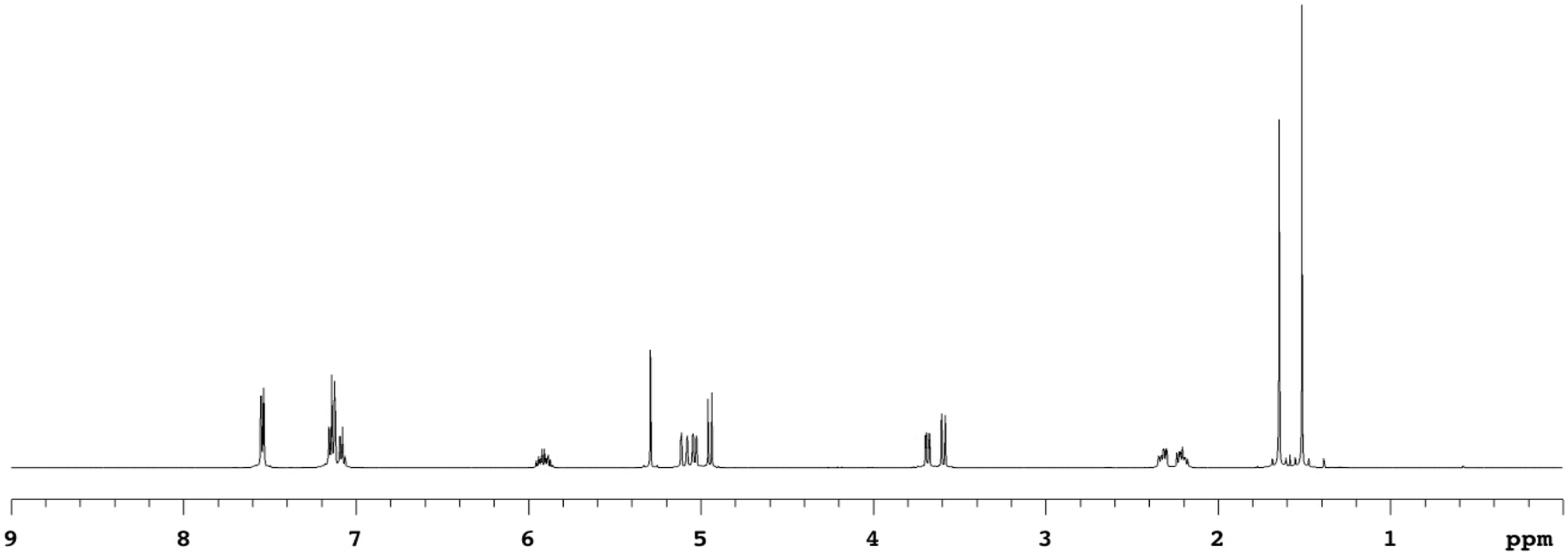
3.131

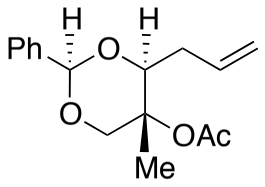
^{13}C NMR, 125 MHz, C_6D_6



3.132

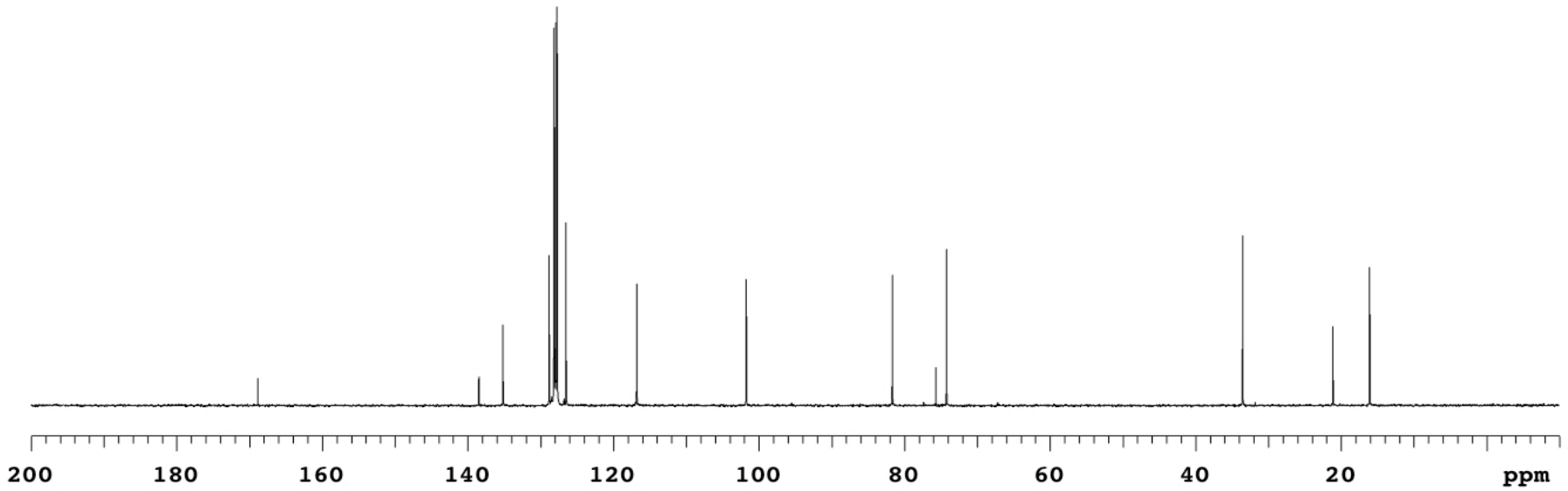
^{1}H NMR, 500 MHz, C_6D_6

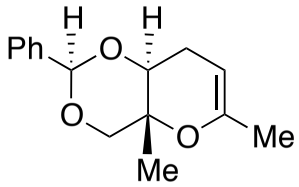




3.132

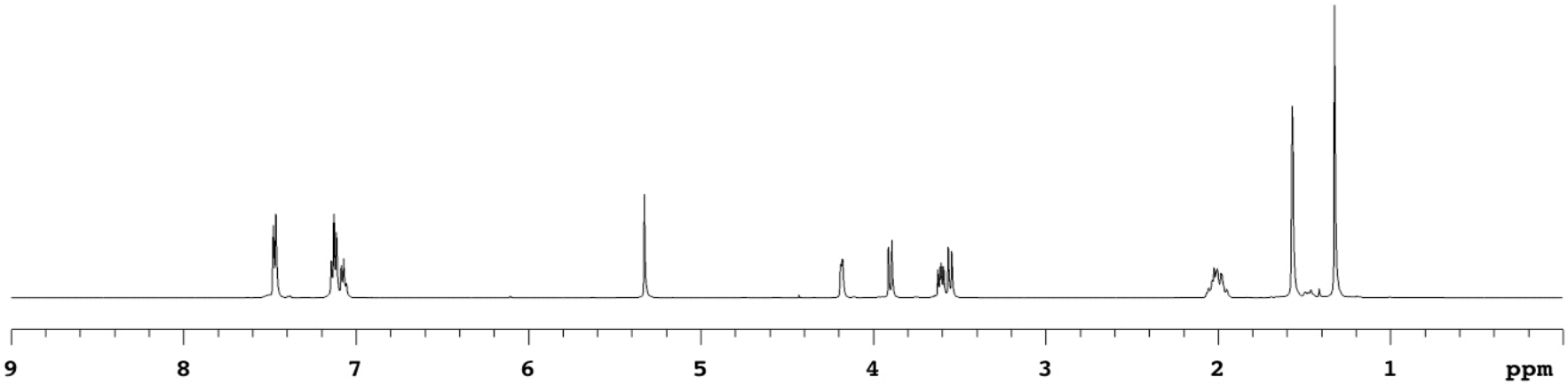
^{13}C NMR, 125 MHz, C_6D_6

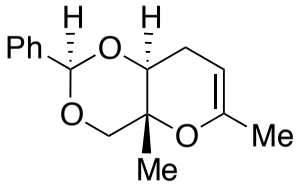




3.133

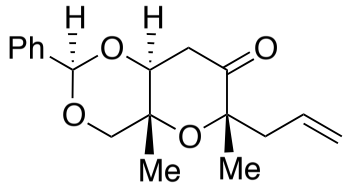
^{1}H NMR, 500 MHz, C_6D_6





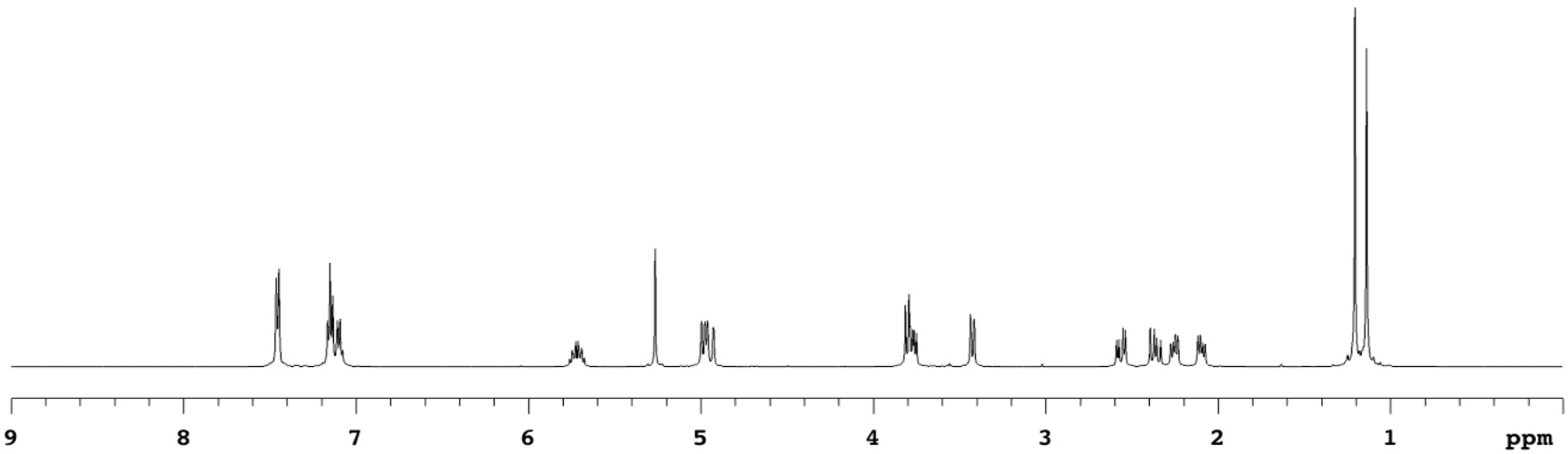
3.133

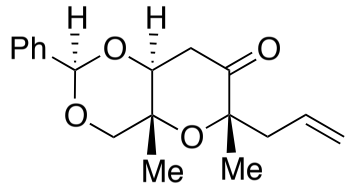
^{13}C NMR, 125 MHz, C_6D_6



3.136

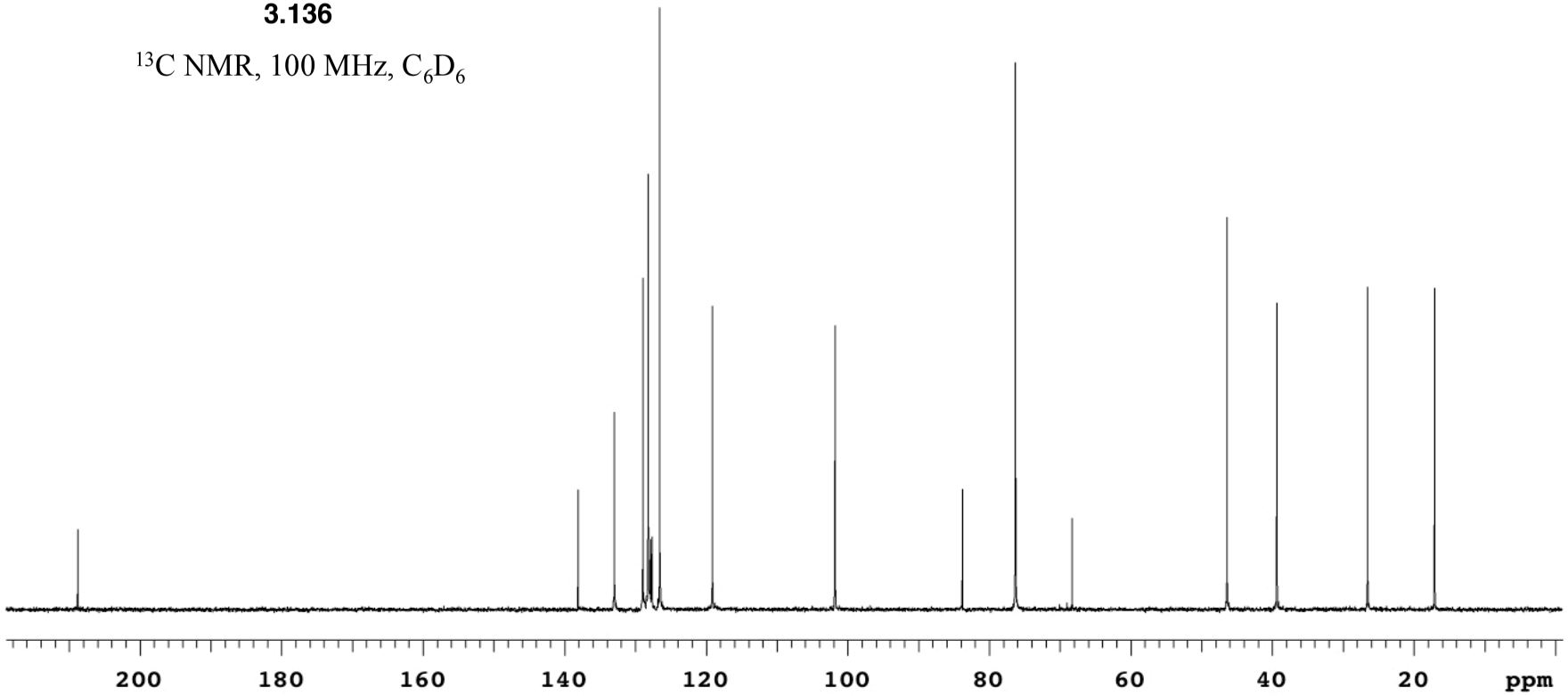
^{1}H NMR, 500 MHz, C_6D_6

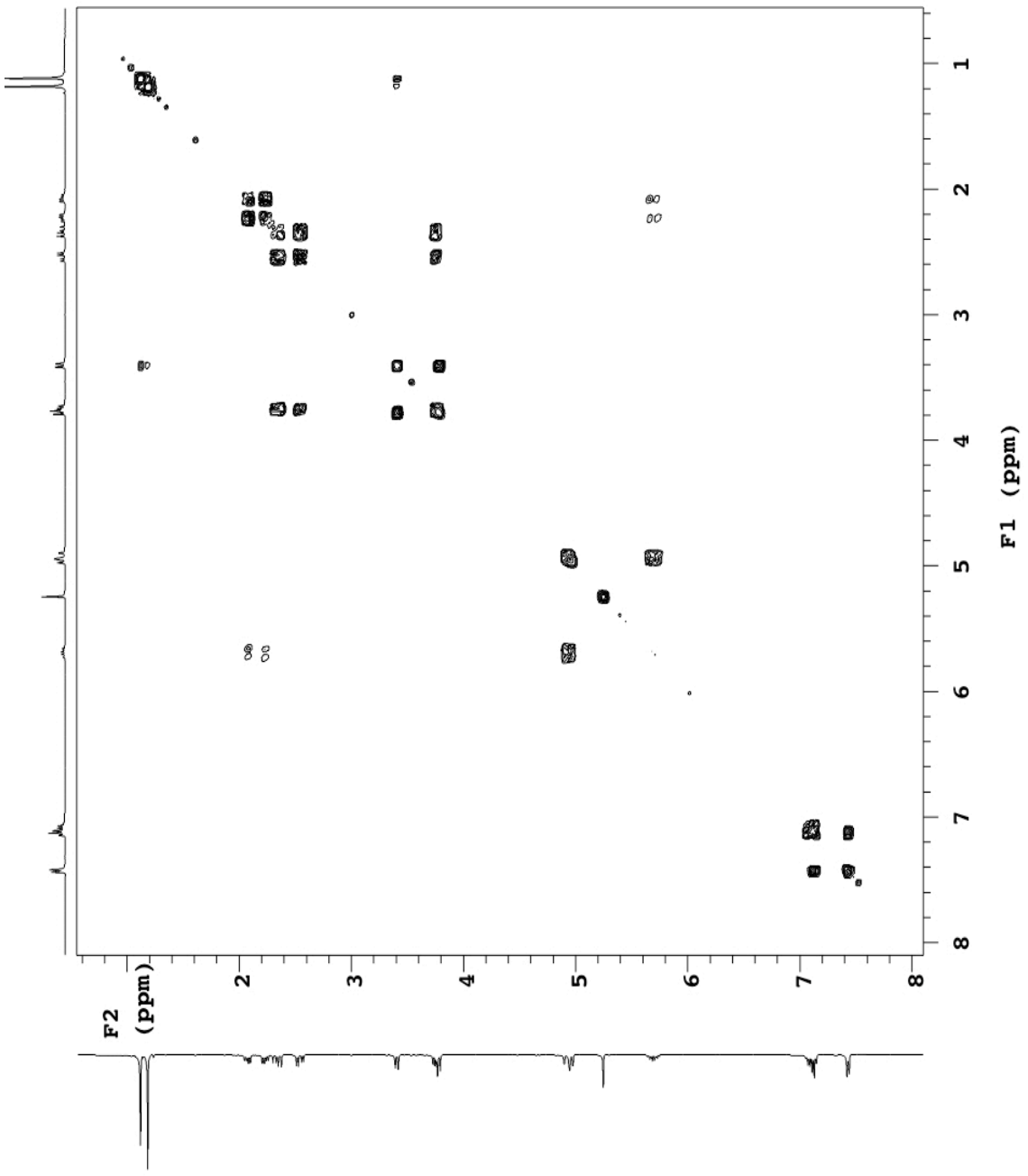


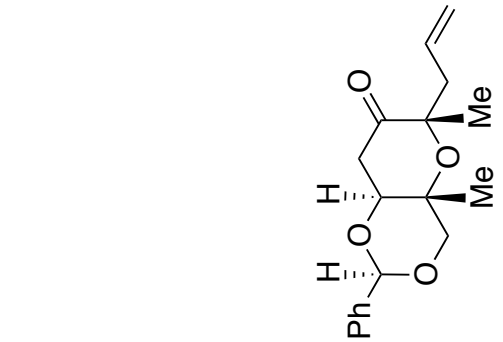


3.136

^{13}C NMR, 100 MHz, C_6D_6

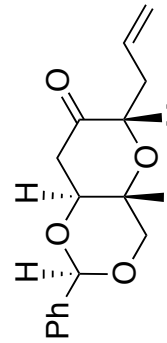






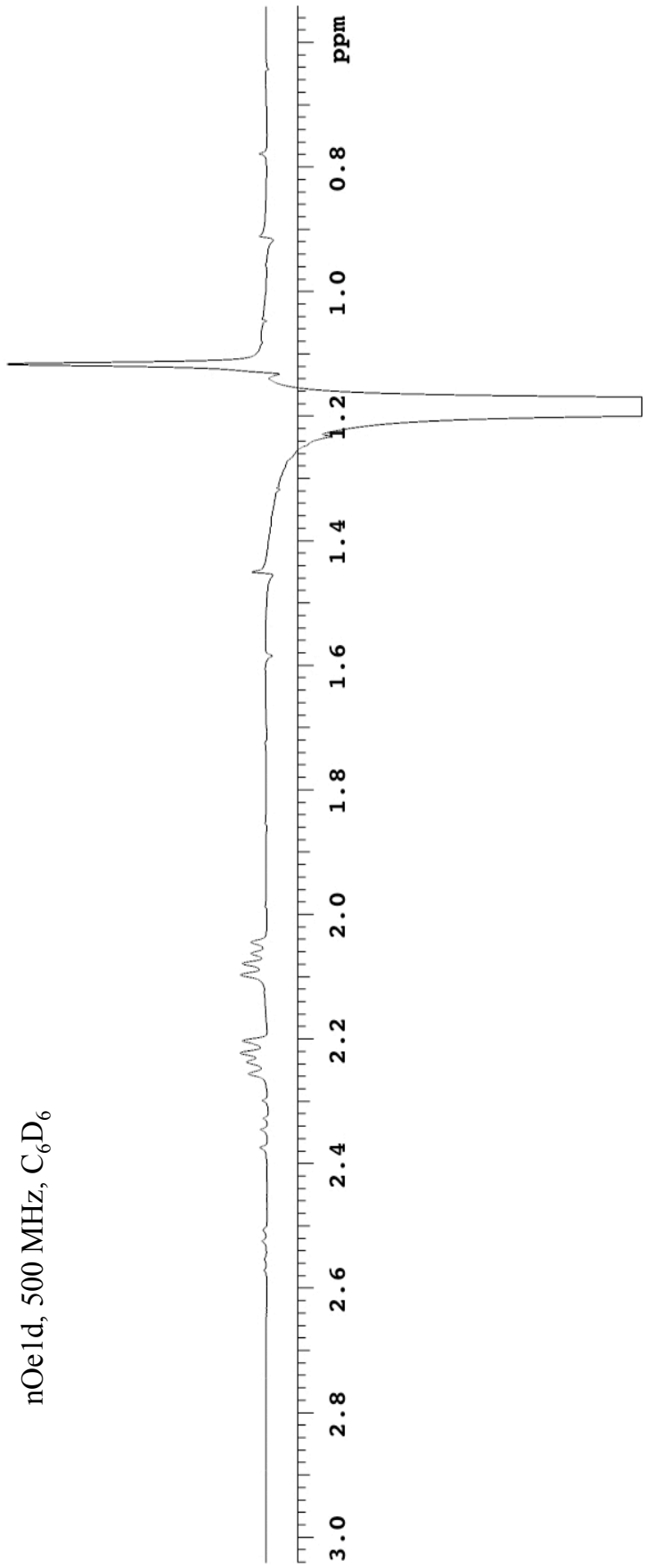
3.136

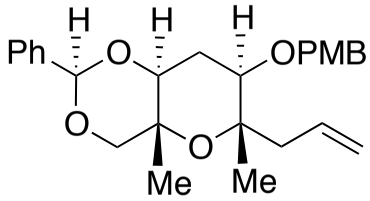
COSY, 500 MHz, C_6D_6



3.136

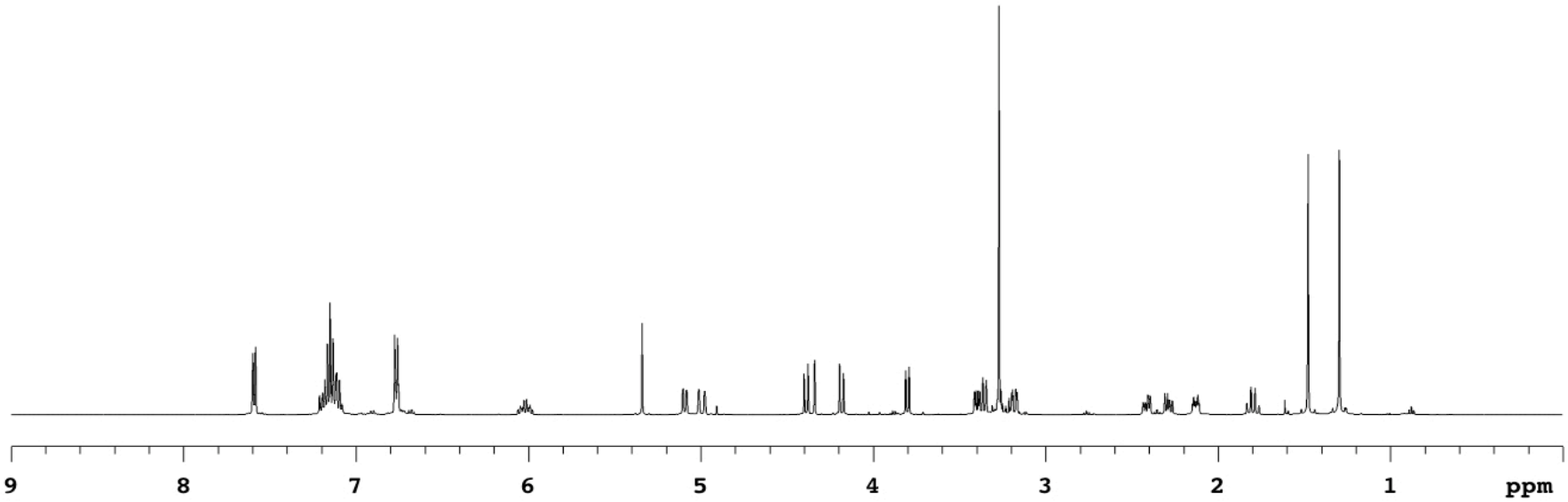
nOe1d, 500 MHz, C_6D_6

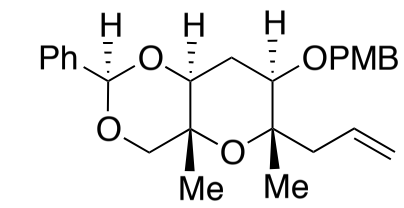




3.138

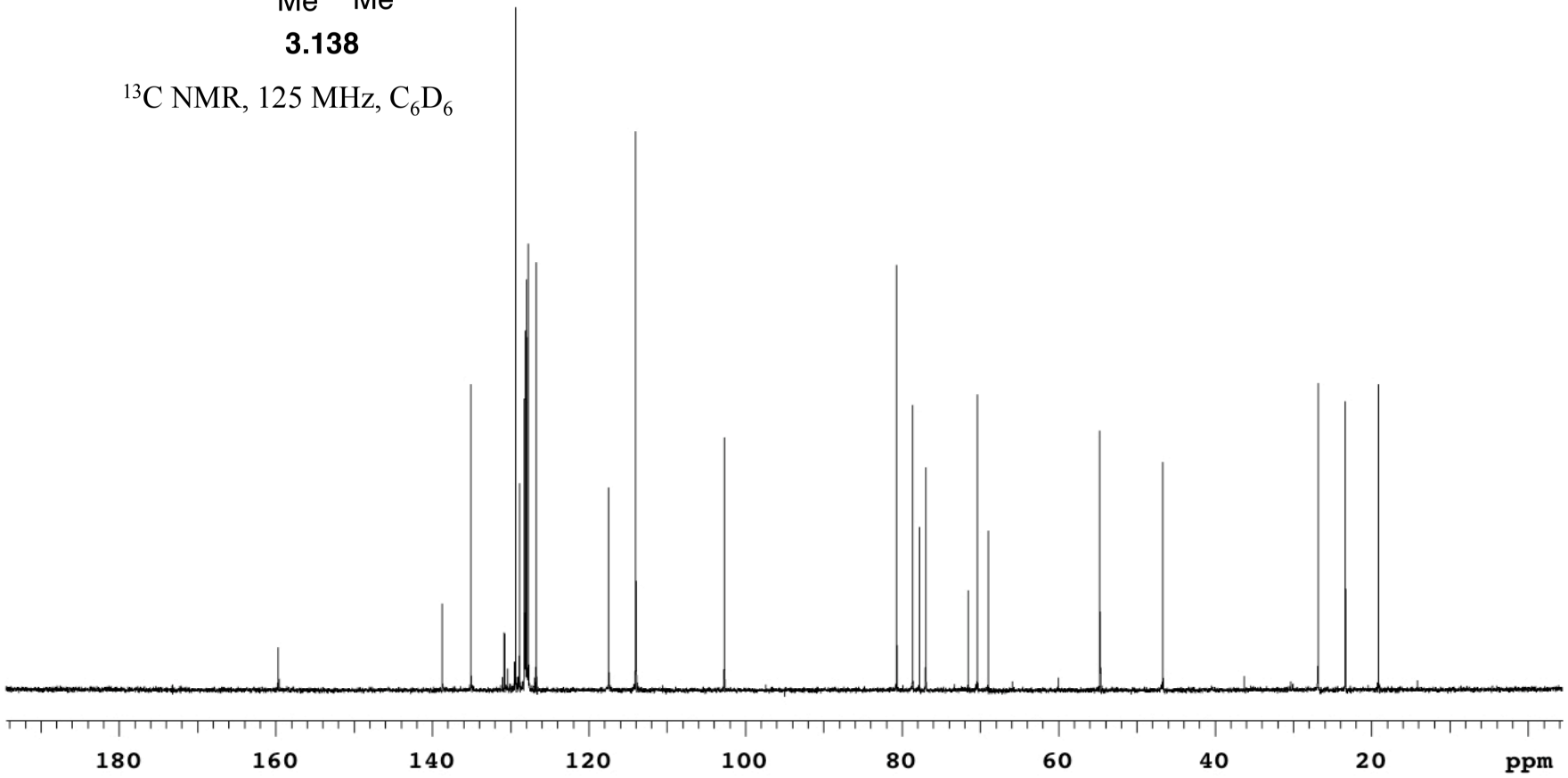
^{1}H NMR, 500 MHz, C_6D_6

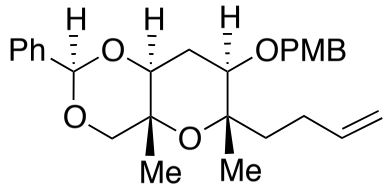




3.138

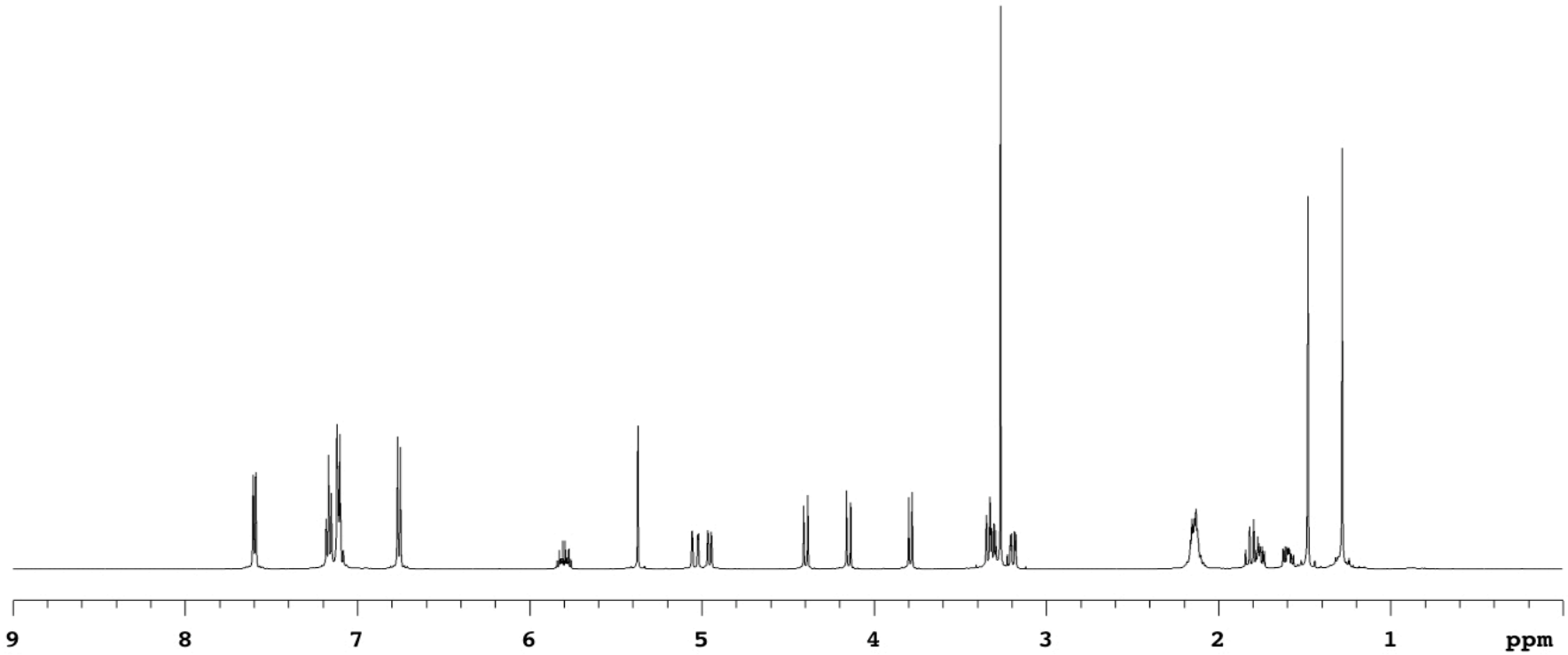
^{13}C NMR, 125 MHz, C_6D_6

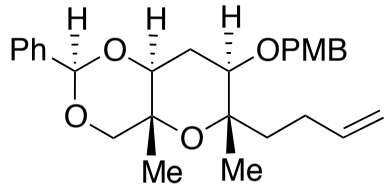




3.139

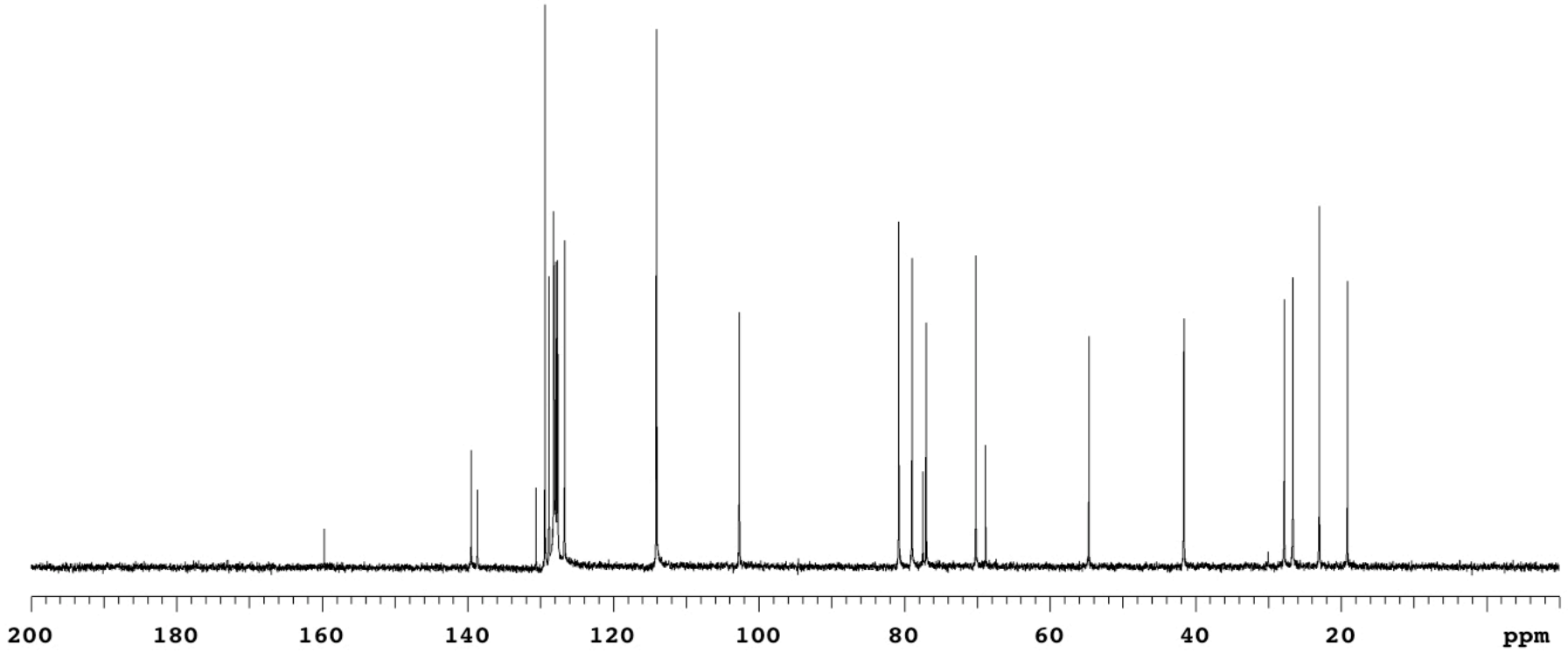
^{1}H NMR, 500 MHz, C_6D_6

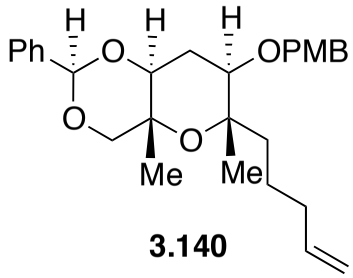




3.139

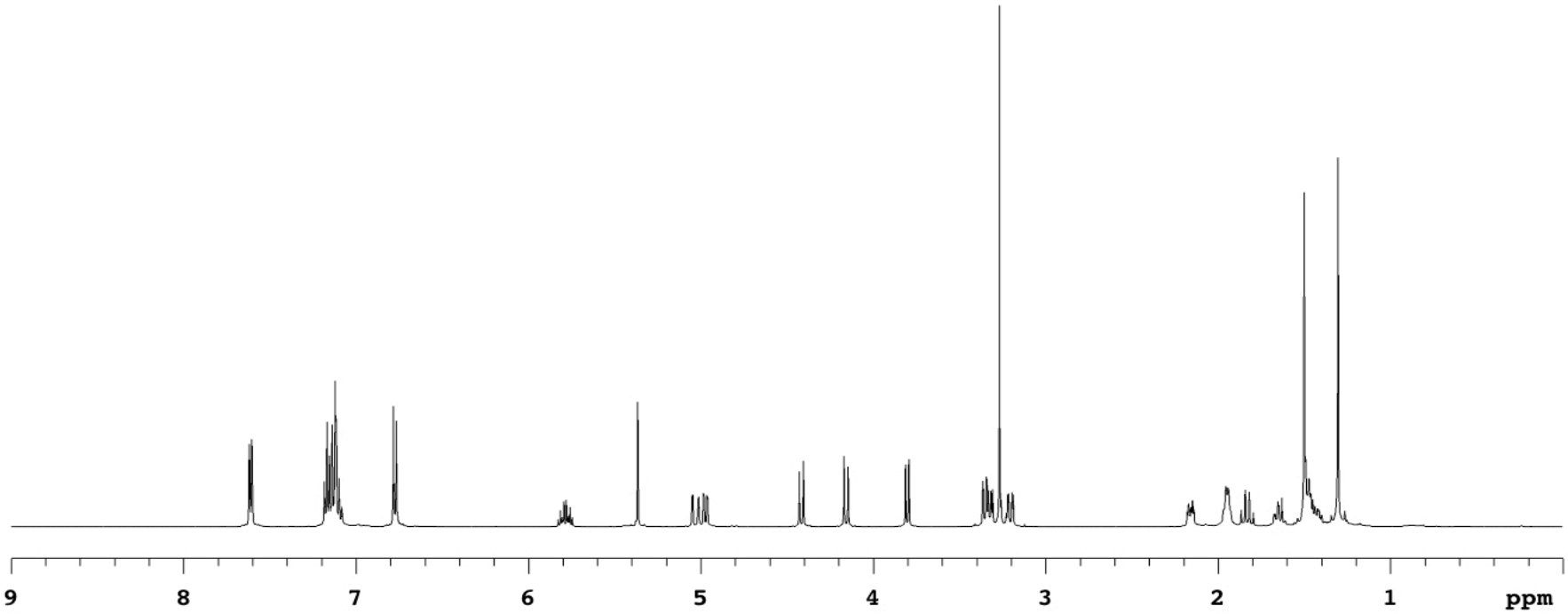
^{13}C NMR, 125 MHz, C_6D_6

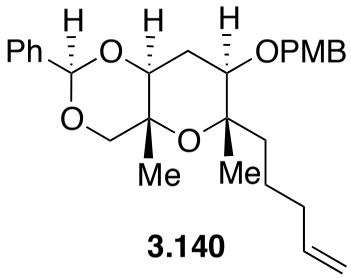




3.140

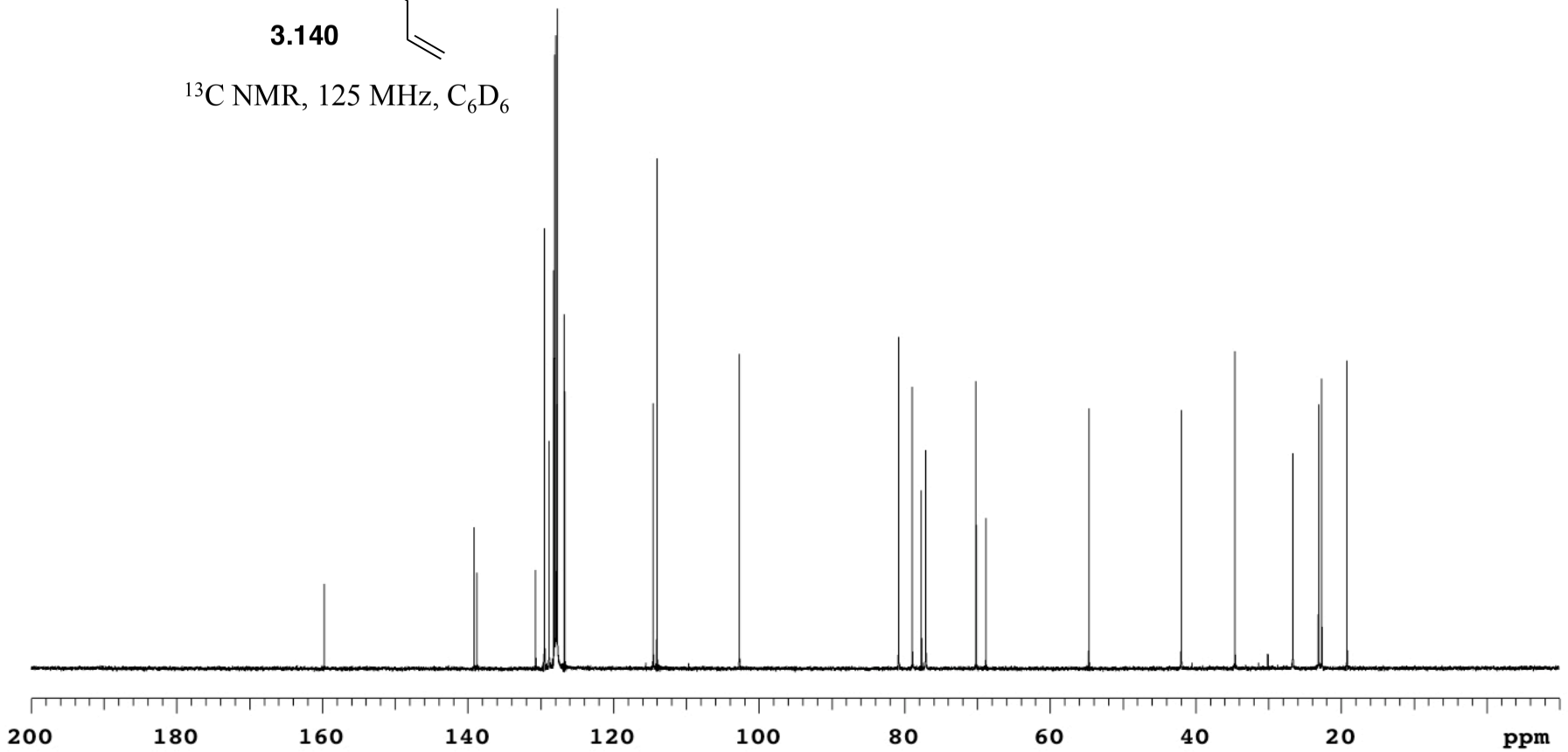
^{1}H NMR, 500 MHz, C_6D_6

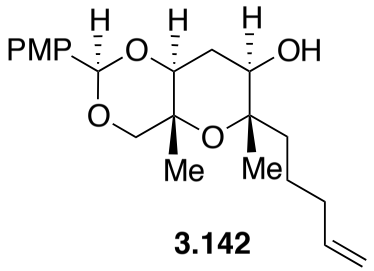




3.140

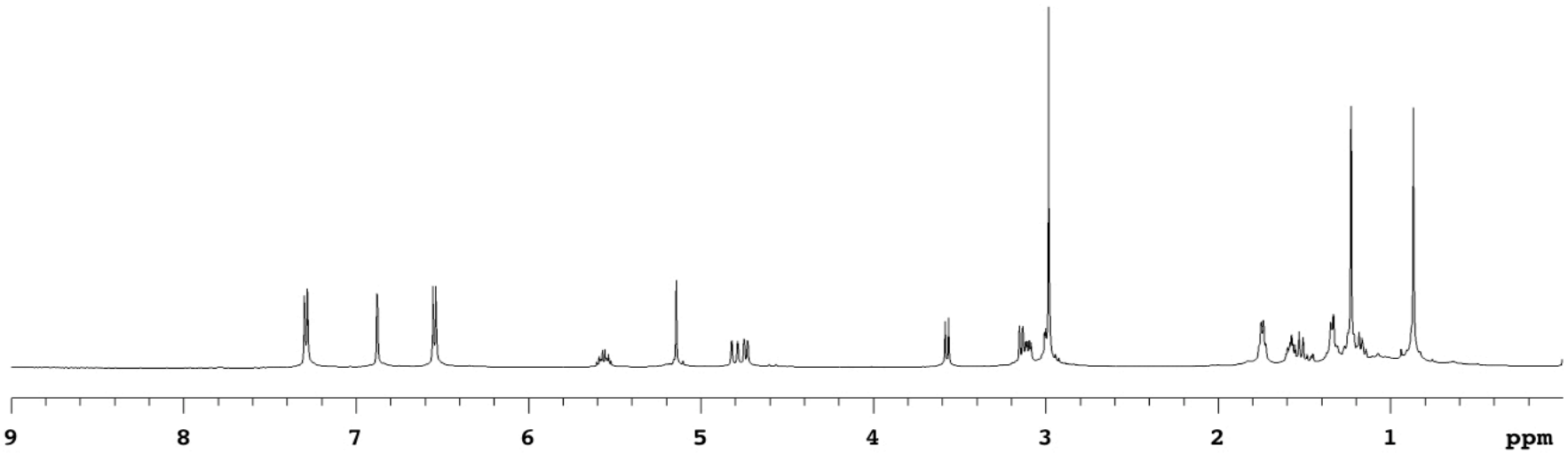
^{13}C NMR, 125 MHz, C_6D_6

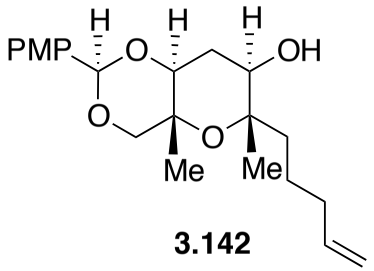




3.142

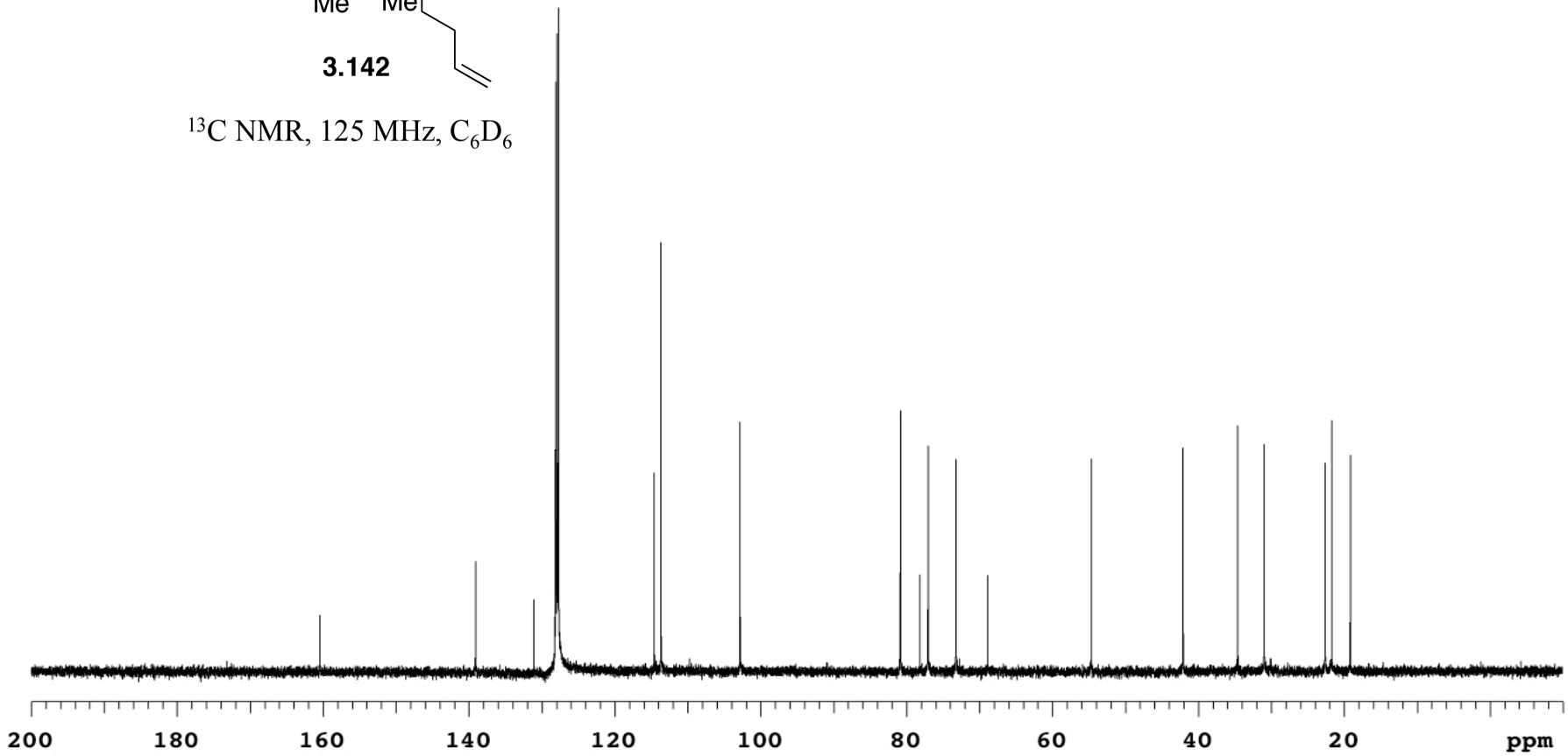
^{1}H NMR, 500 MHz, C_6D_6

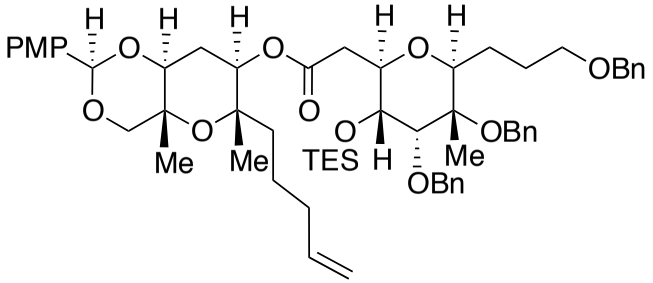




3.142

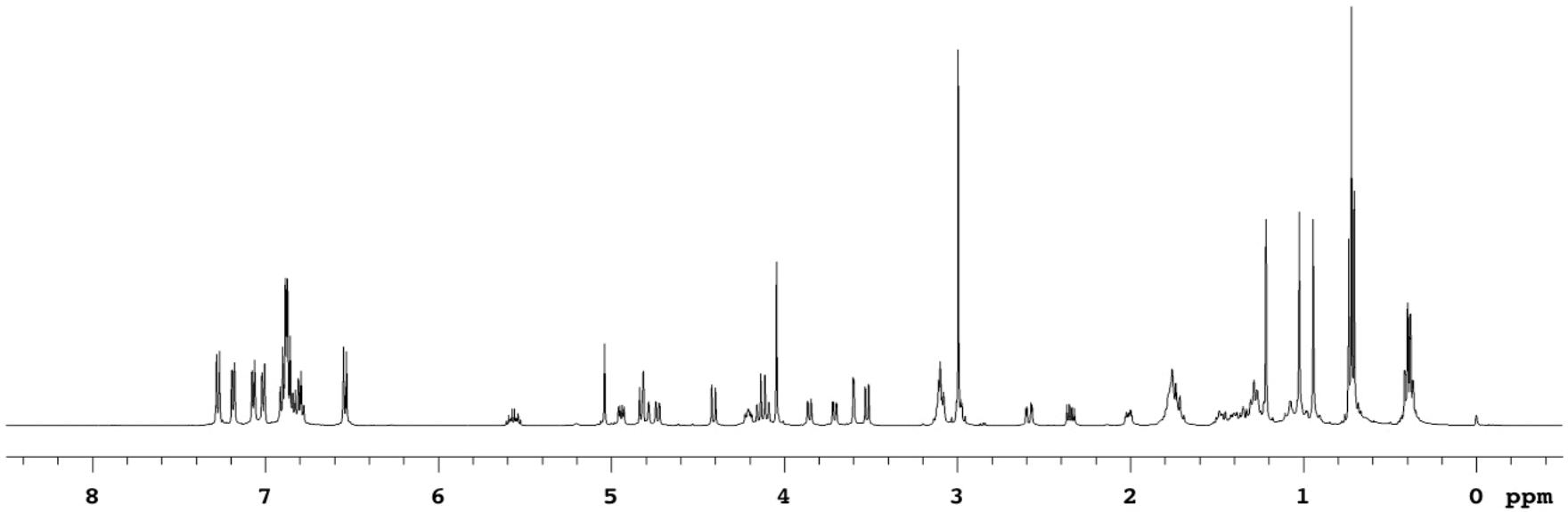
^{13}C NMR, 125 MHz, C_6D_6

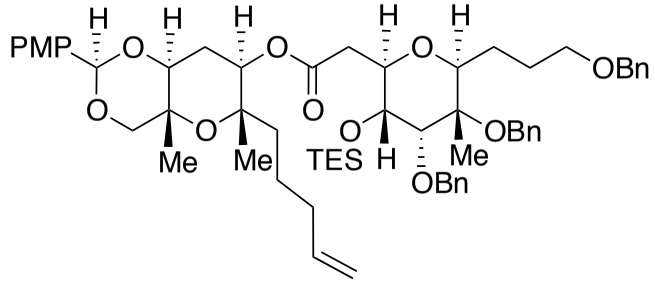




3.143

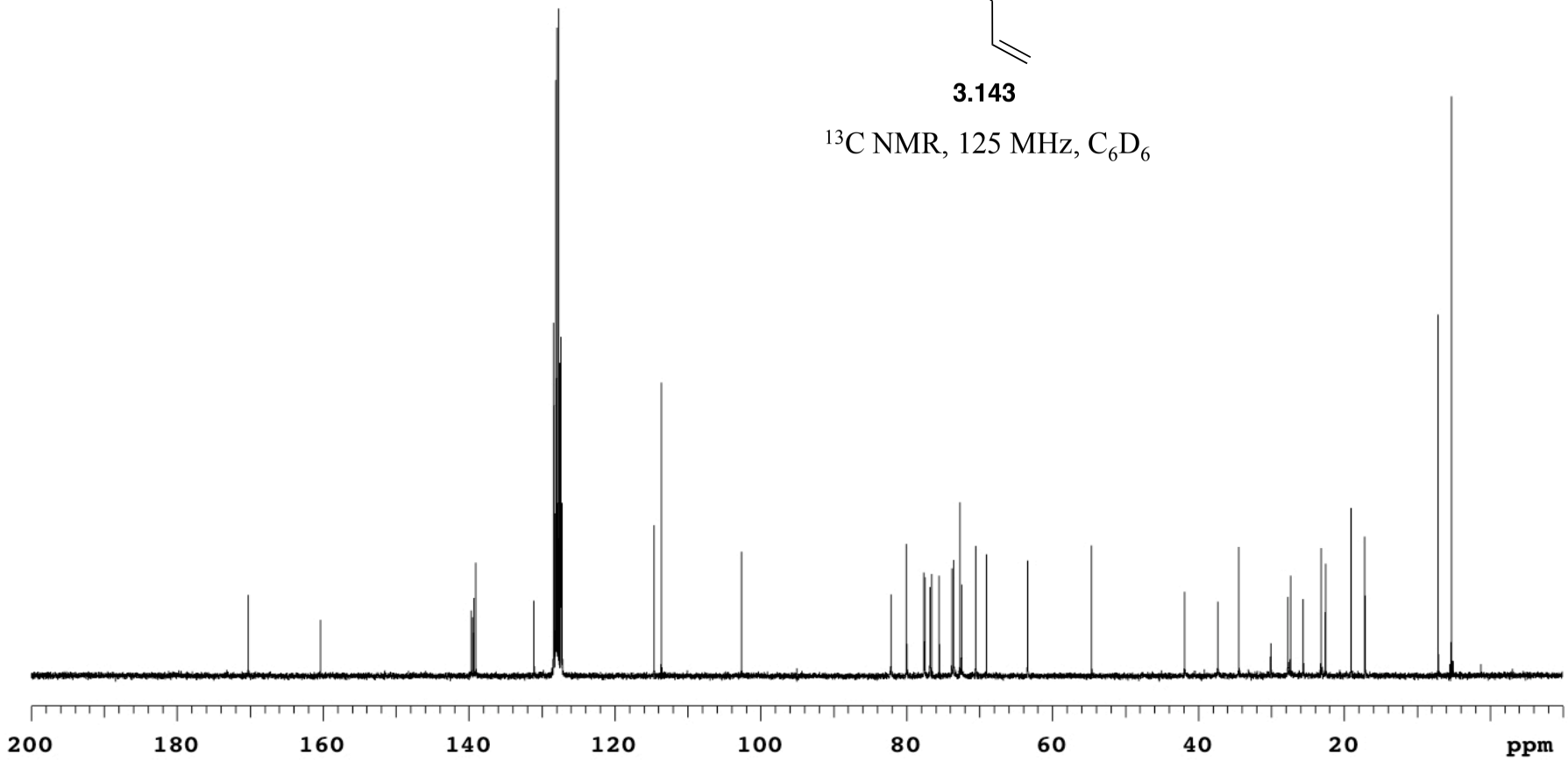
^{1}H NMR, 500 MHz, C_6D_6

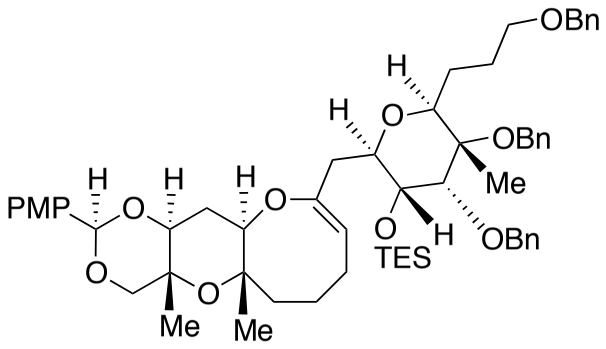




3.143

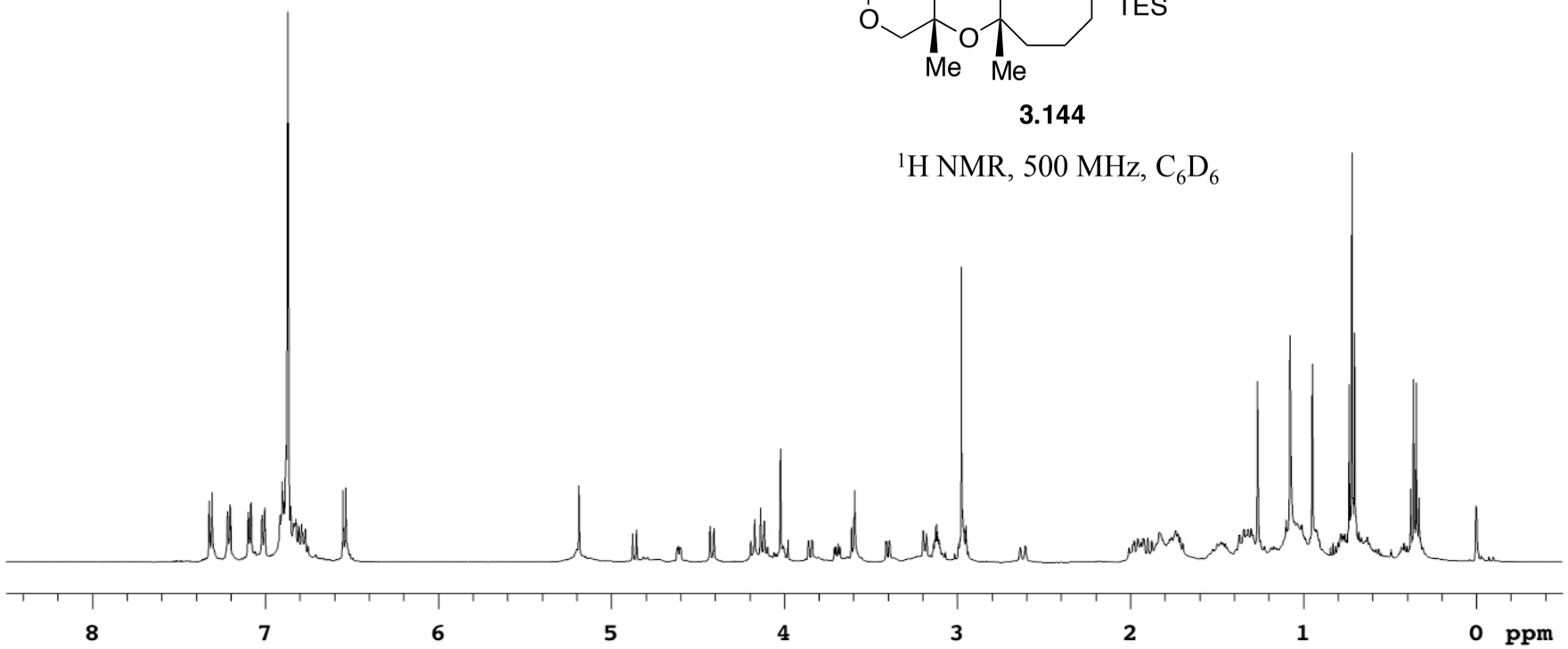
^{13}C NMR, 125 MHz, C_6D_6

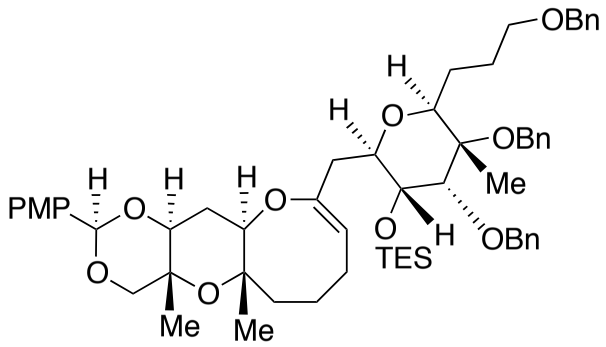




3.144

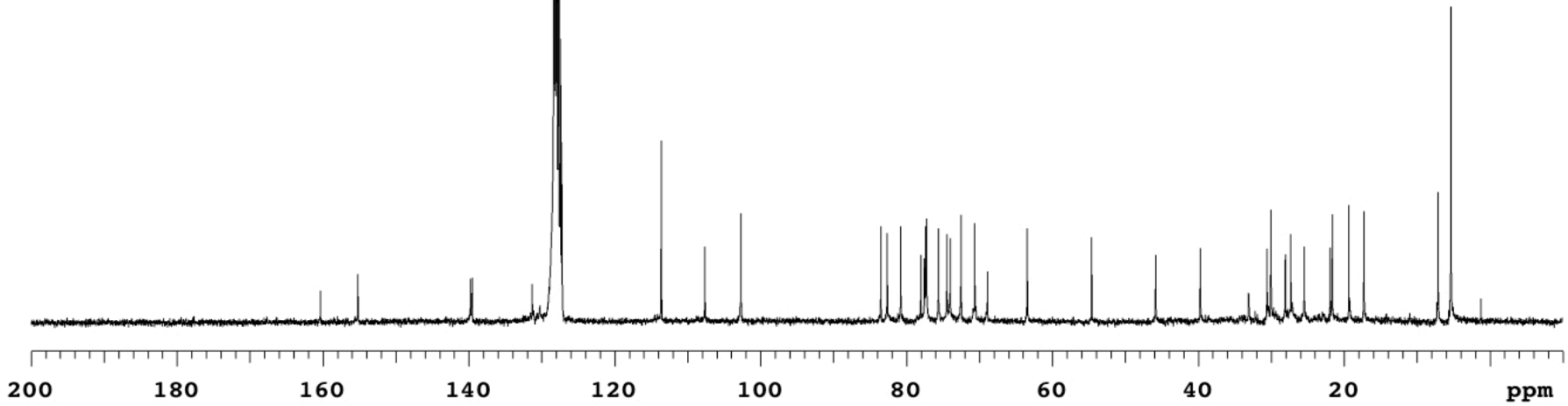
^{1}H NMR, 500 MHz, C_6D_6

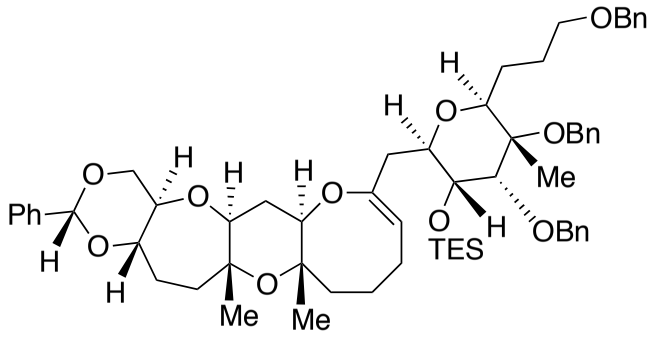




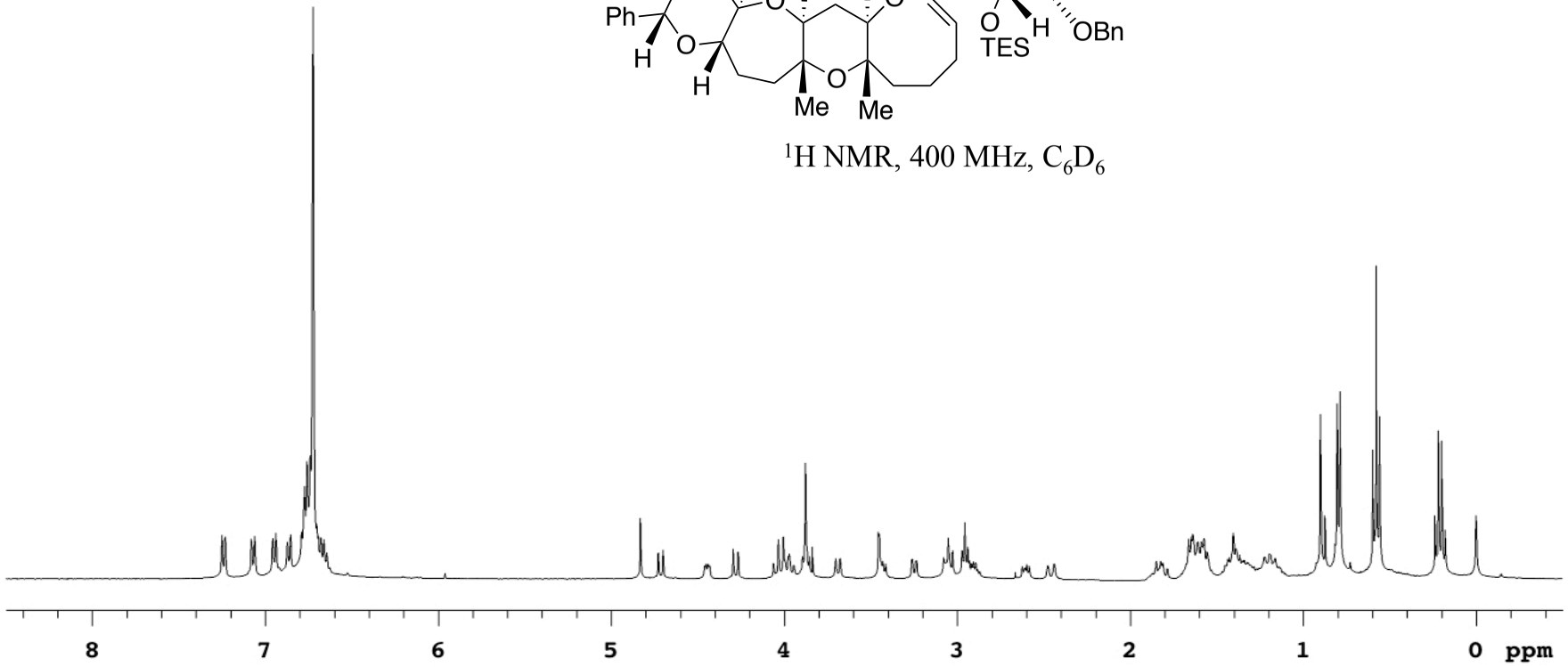
3.144

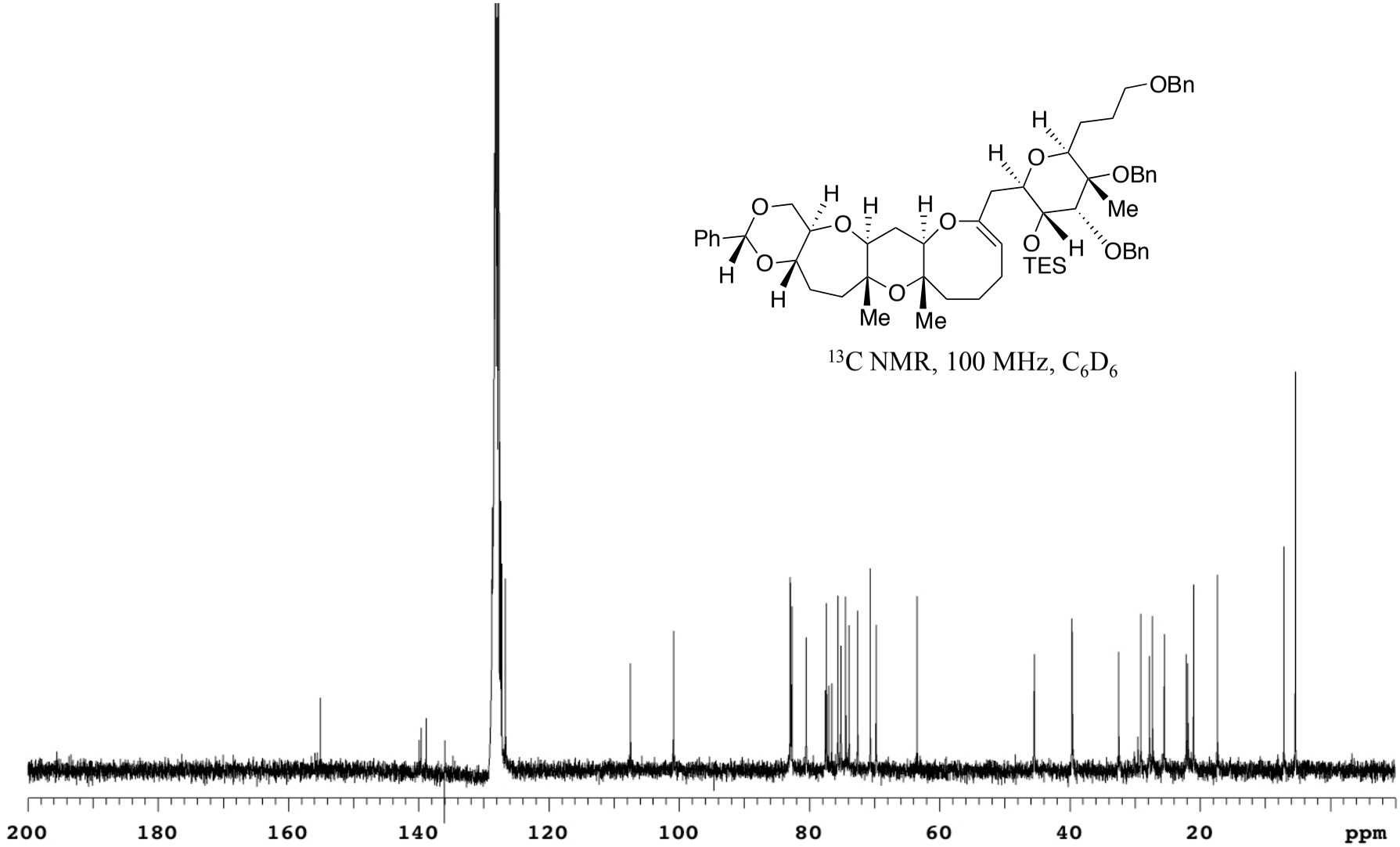
^{13}C NMR, 100 MHz, C_6D_6



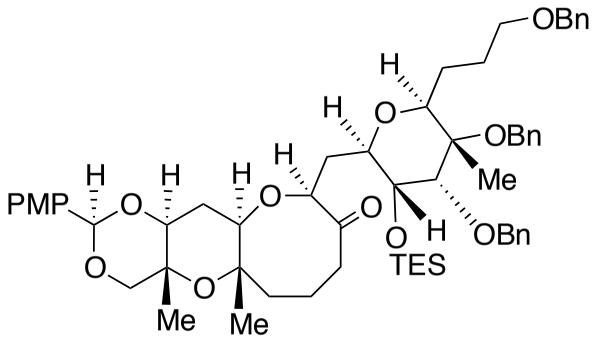


^{1}H NMR, 400 MHz, C_6D_6



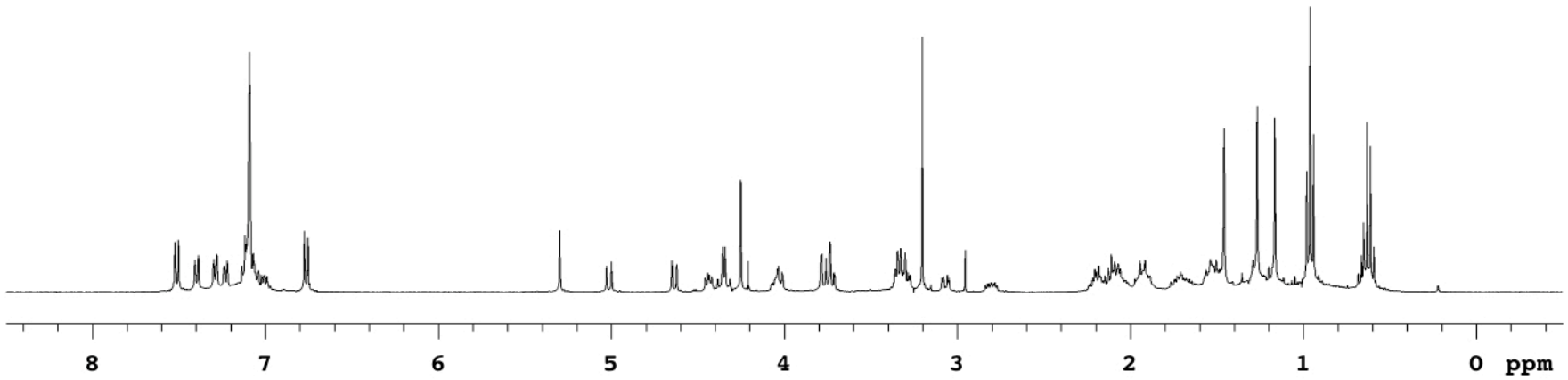


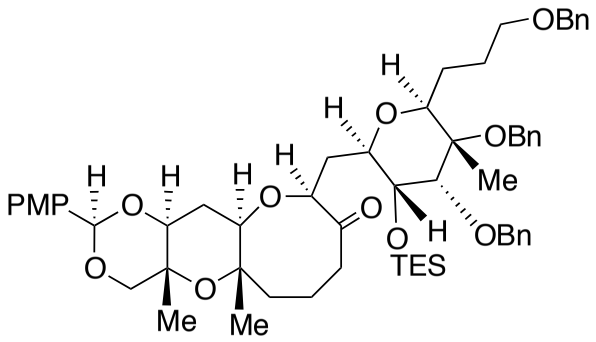
^{13}C NMR, 100 MHz, C_6D_6



3.150

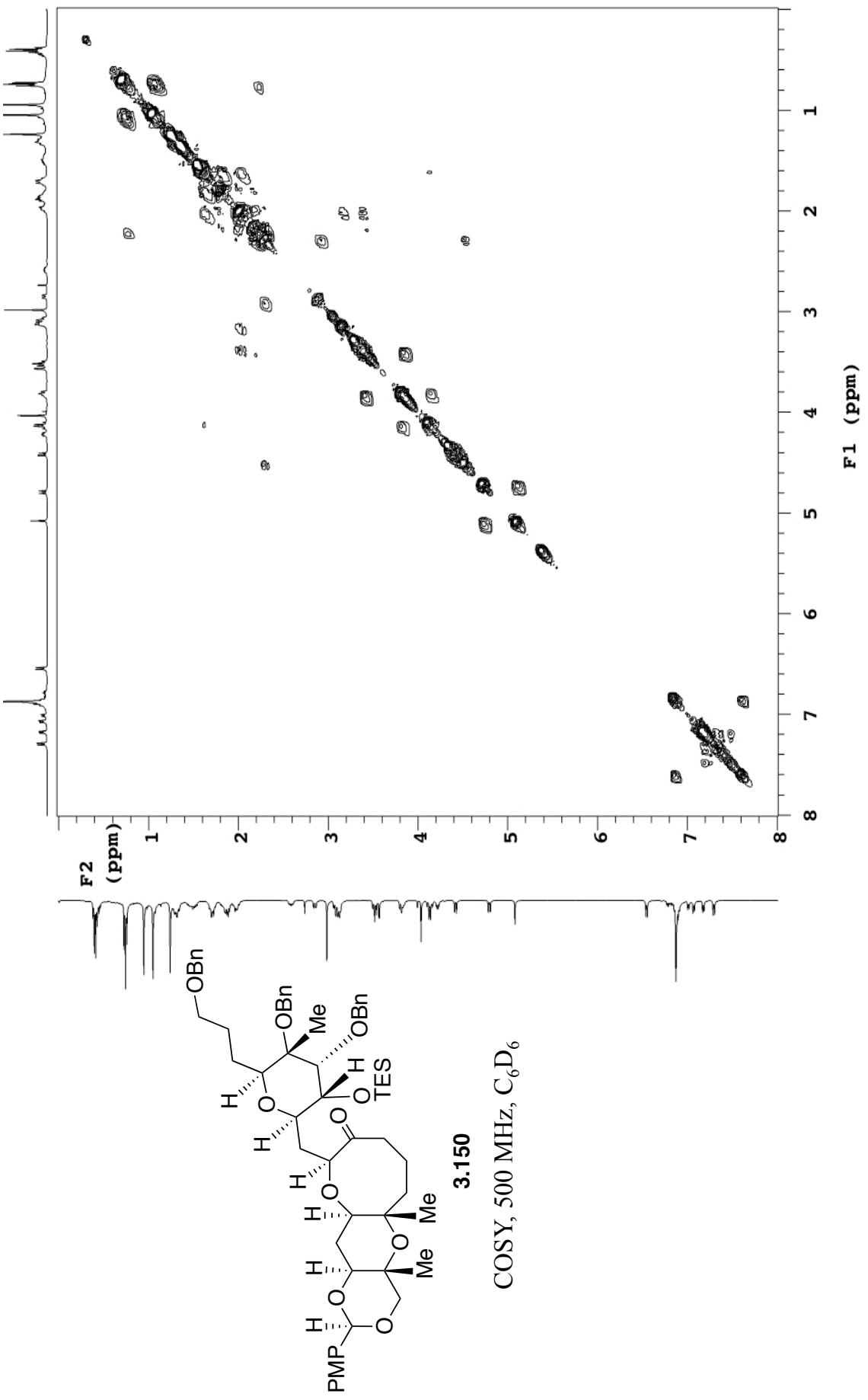
^{1}H NMR, 500 MHz, C_6D_6





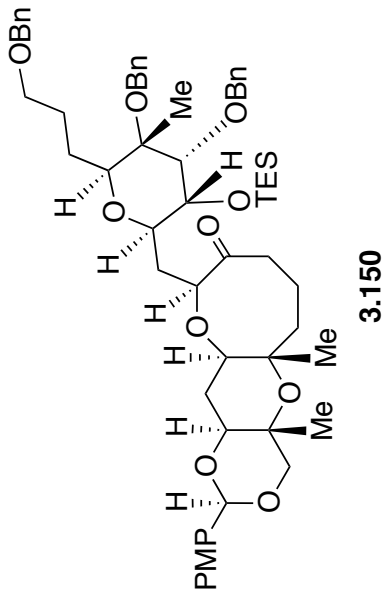
3.150

^{13}C NMR, 100 MHz, C_6D_6



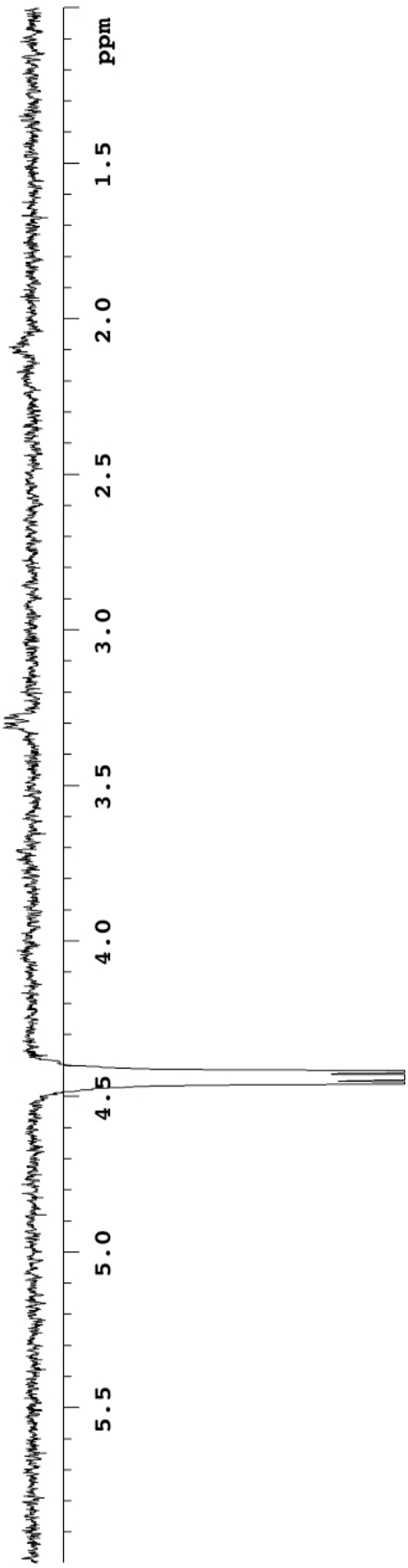
3.150

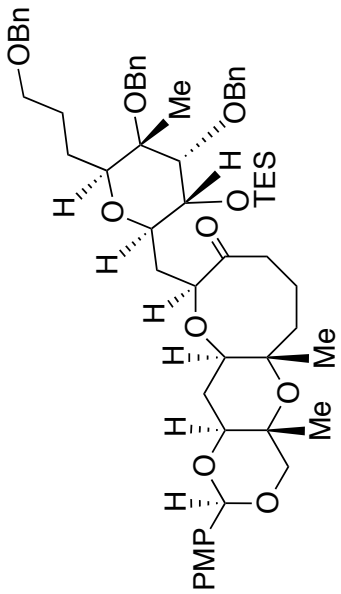
COSY, 500 MHz, C_6D_6



3.150

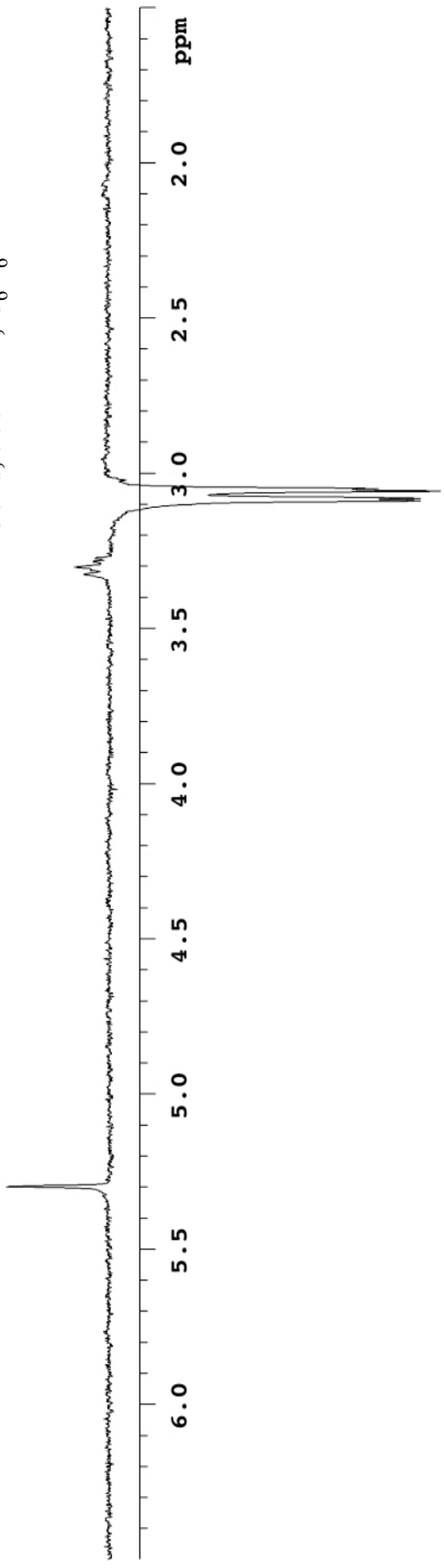
nOe1d, 500 MHz, C_6D_6

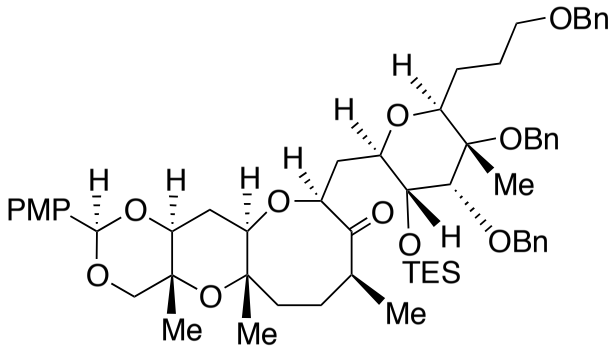




3.150

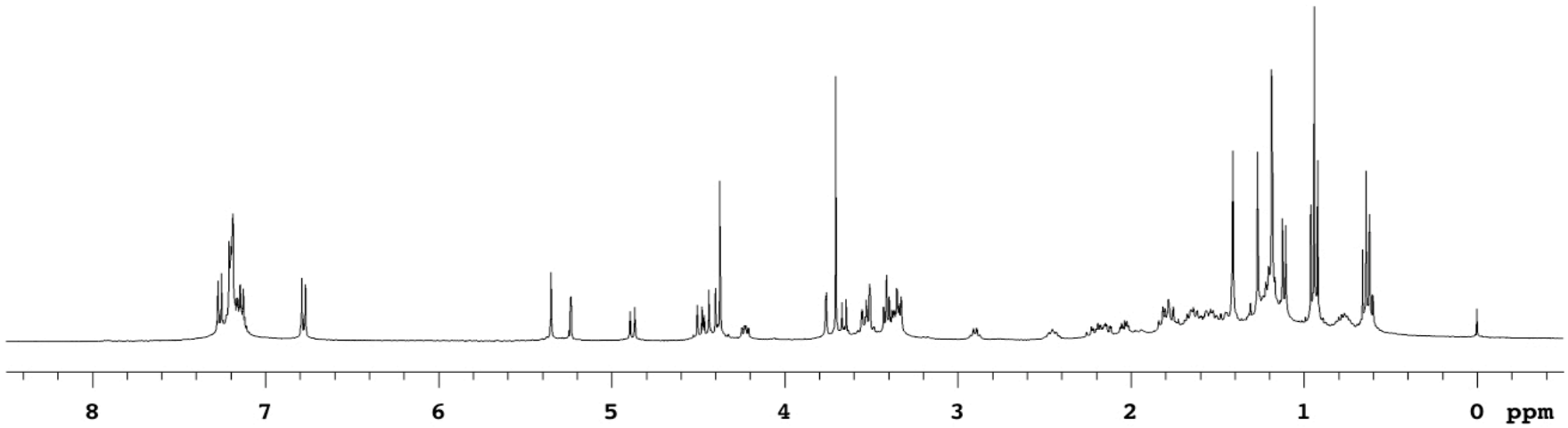
nOe1d, 500 MHz, C_6D_6

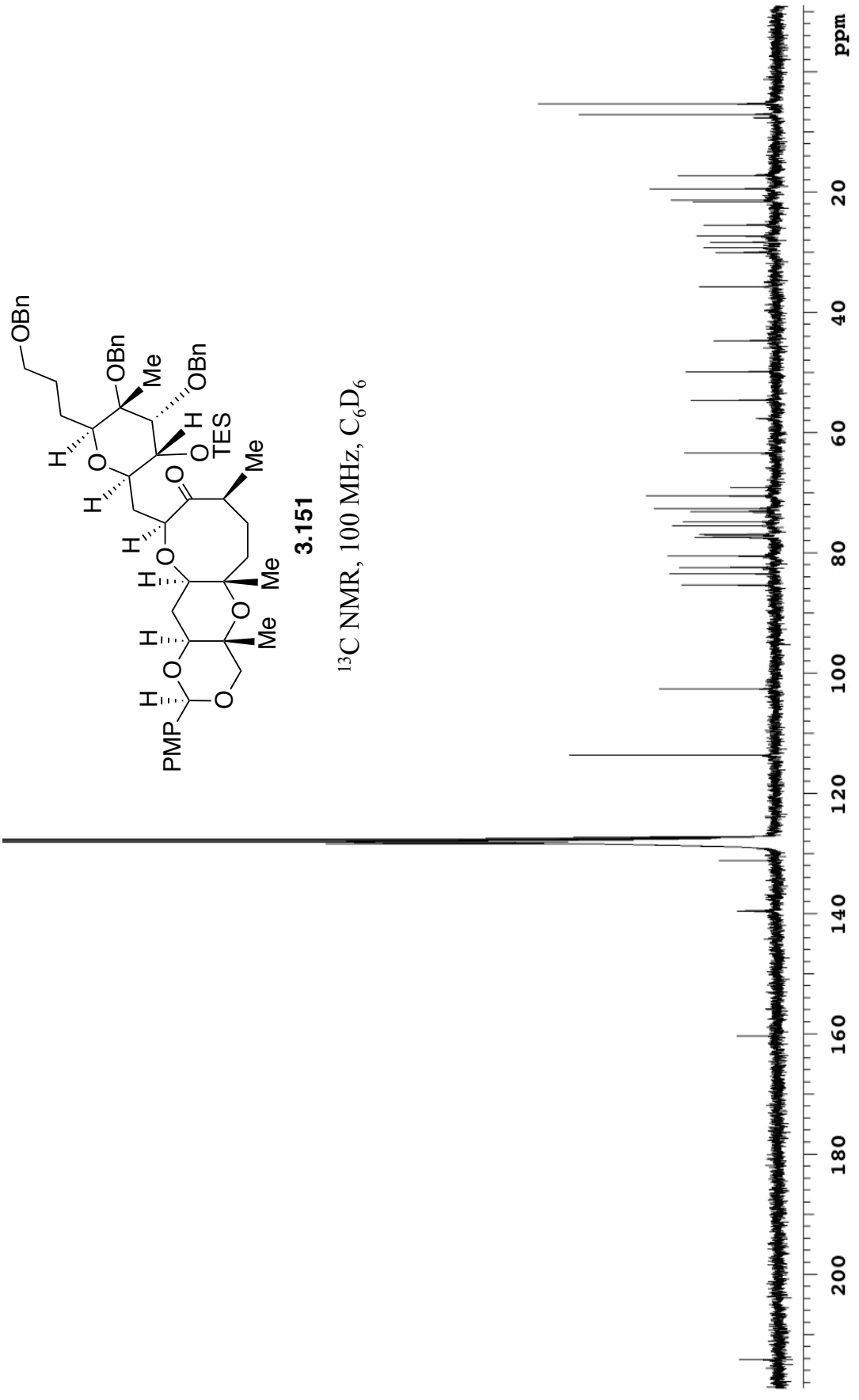




3.151

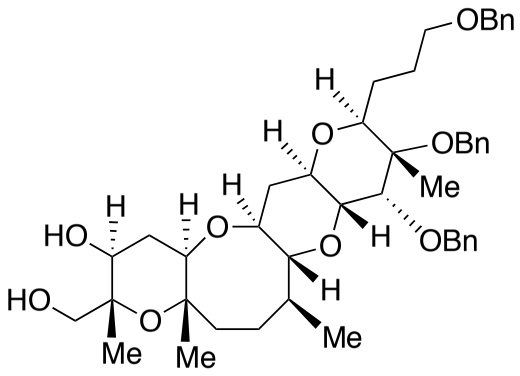
^{1}H NMR, 400 MHz, CD_2Cl_2





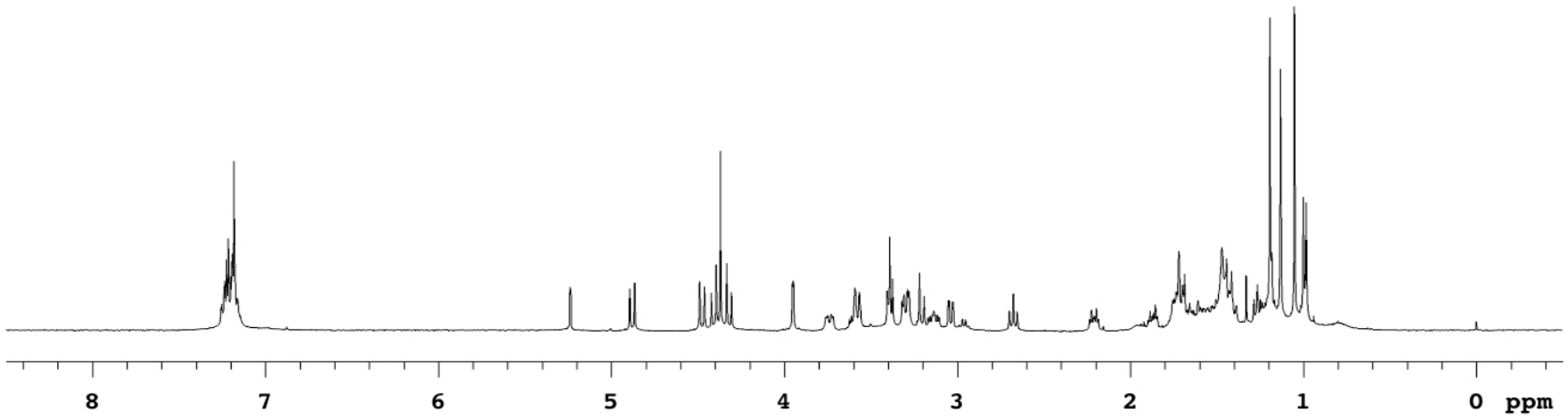
3.151

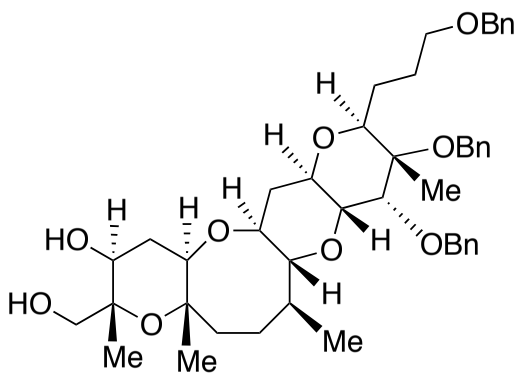
^{13}C NMR, 100 MHz, C_6D_6



3.152

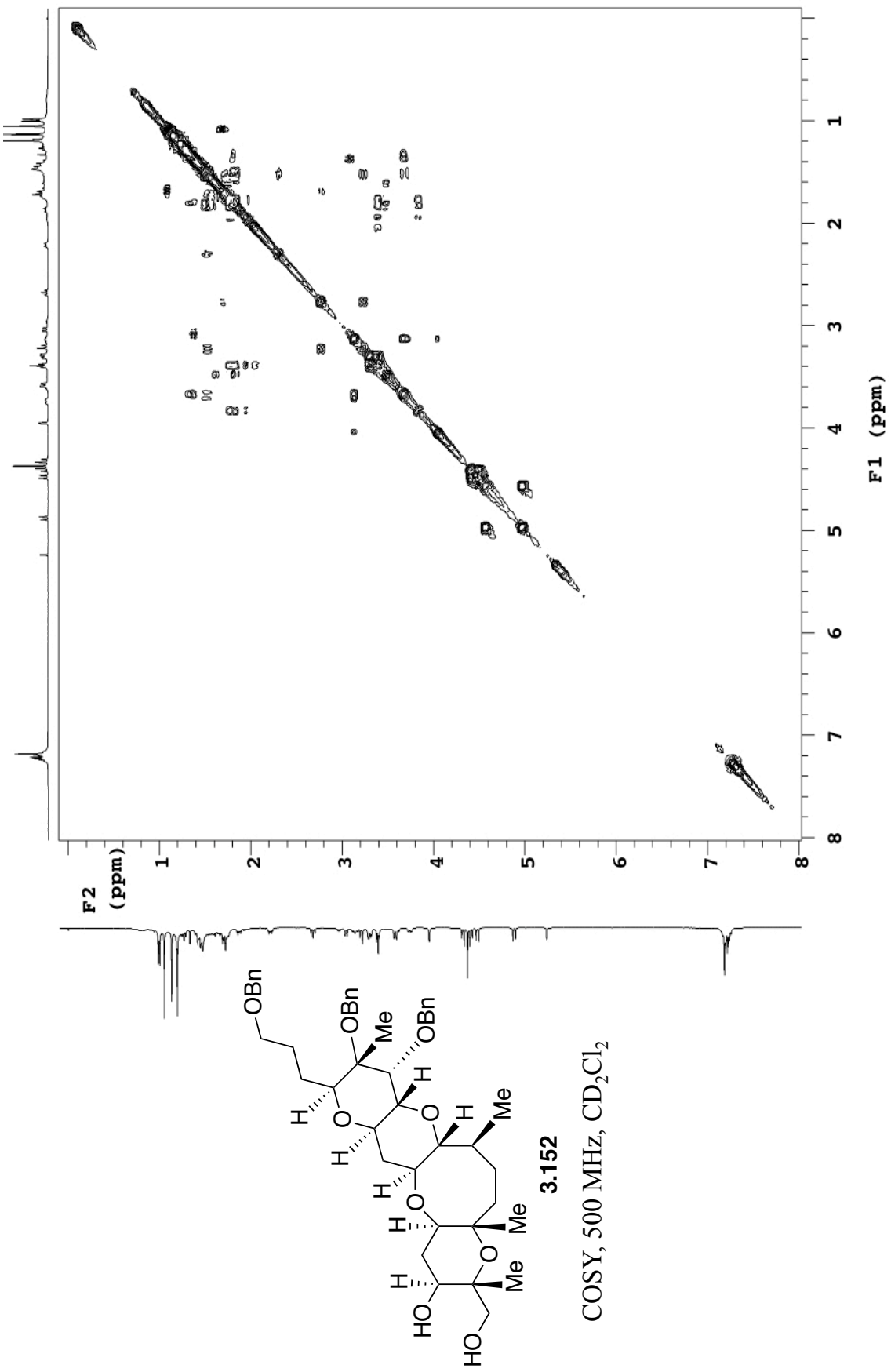
^{1}H NMR, 500 MHz, CD_2Cl_2





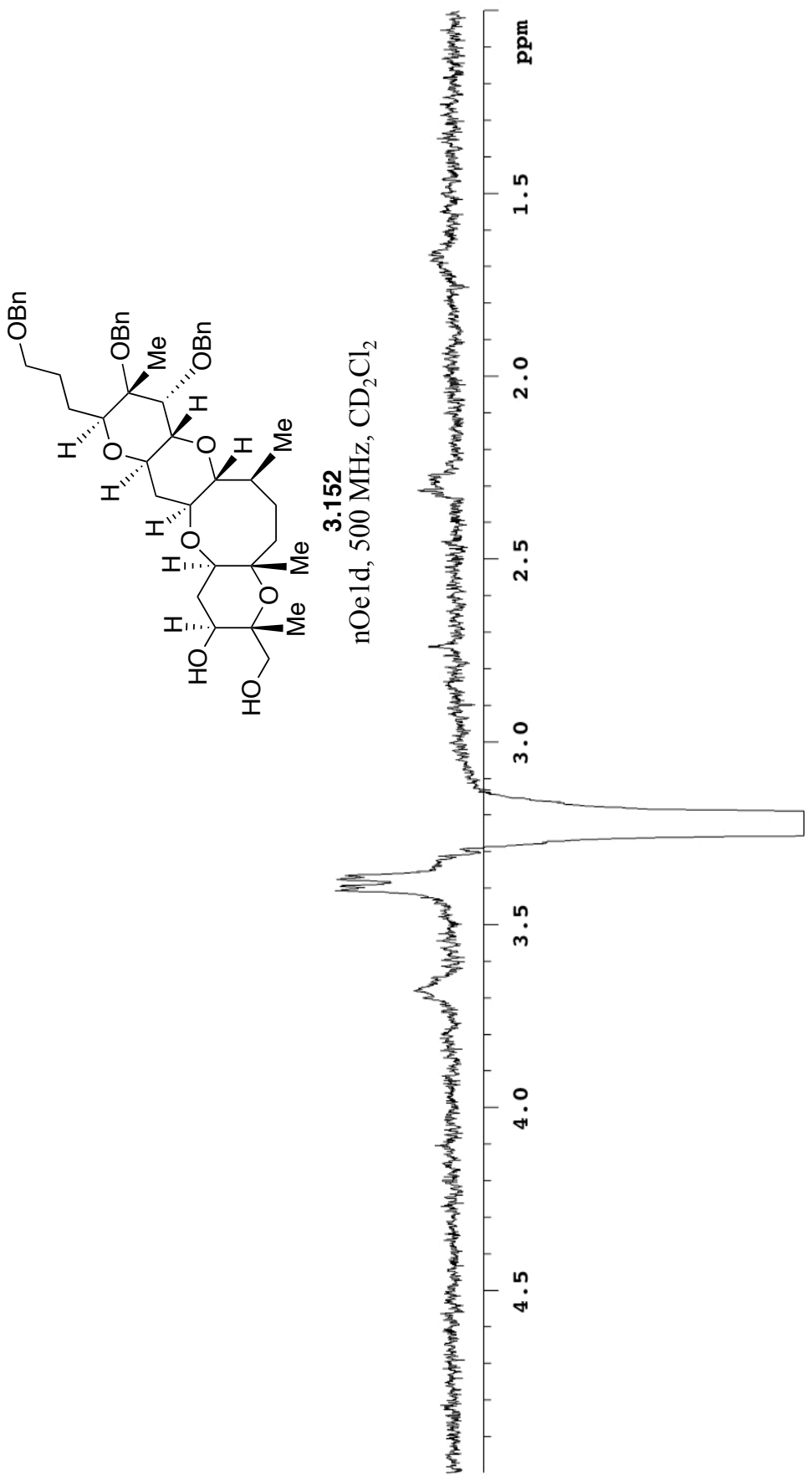
3.152

^{13}C NMR, 100 MHz, C_6D_6

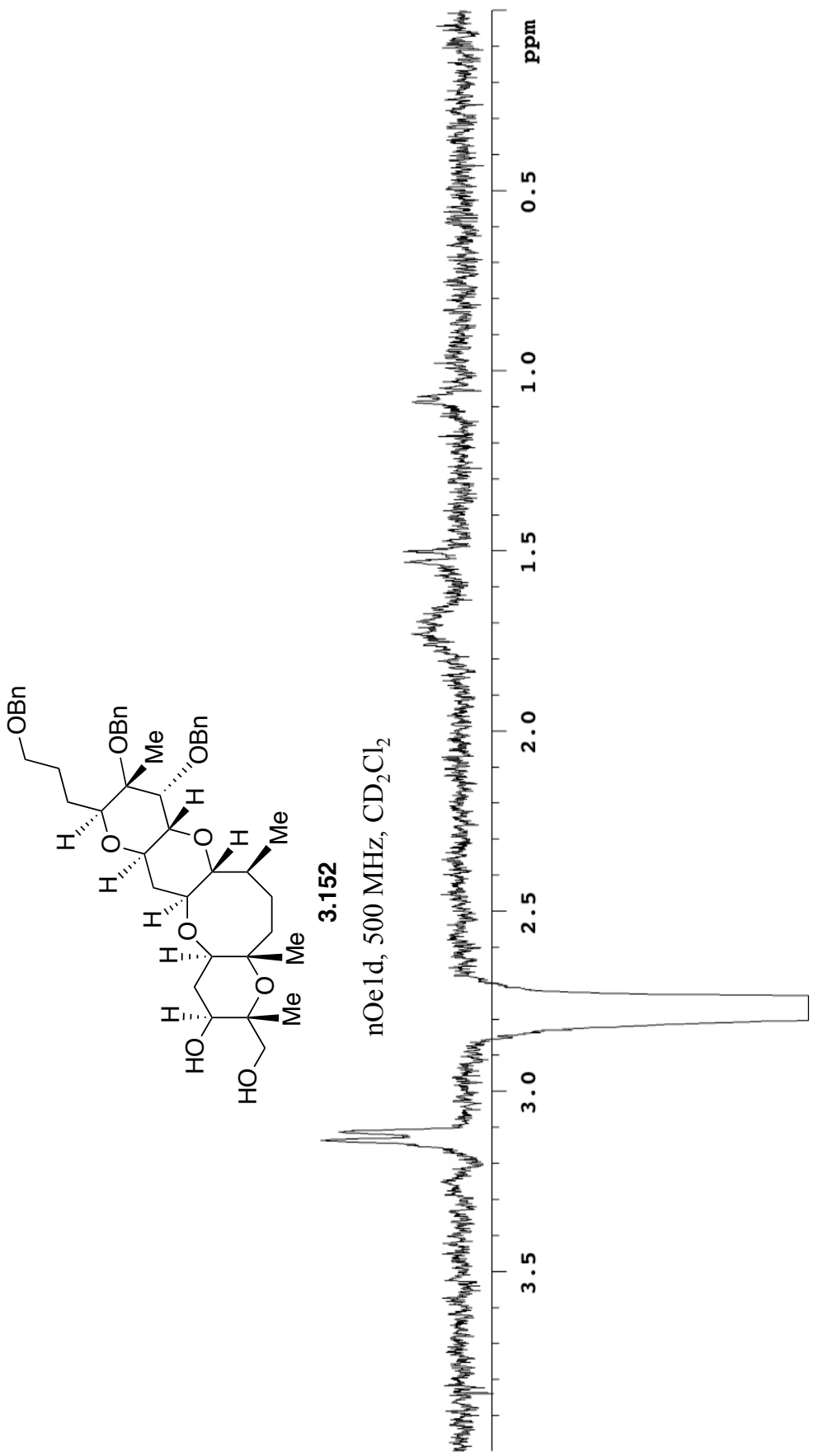


3.152

COSY, 500 MHz, CD_2Cl_2



3.152
nOe1d, 500 MHz, CD_2Cl_2


OBn
OBn
Me
OBn
H
O
H
H
O
H
Me
H
O
Me
Me
O
Me
H
HO
HO
3.152
nOe1d, 500 MHz, CD_2Cl_2
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm